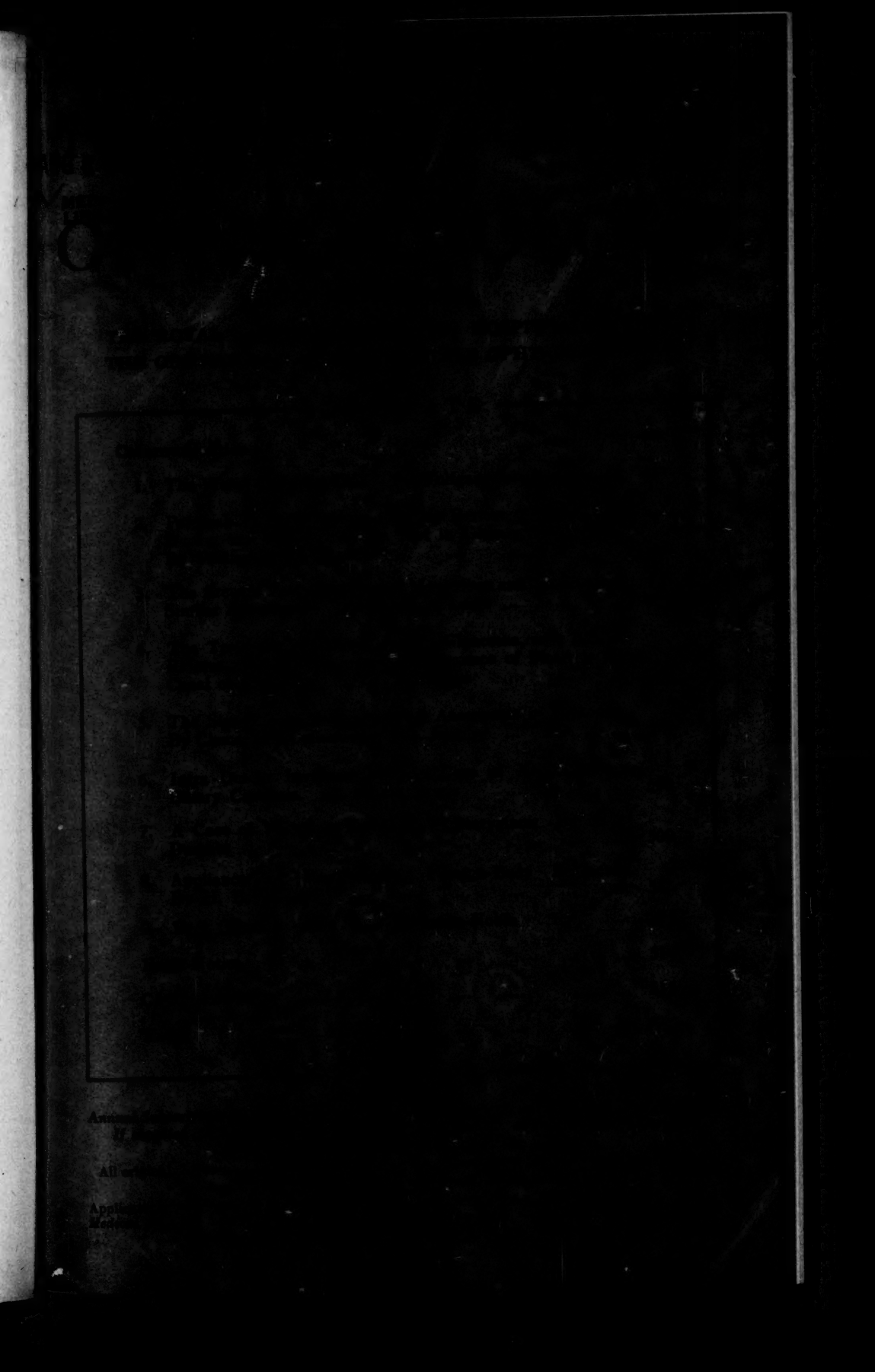

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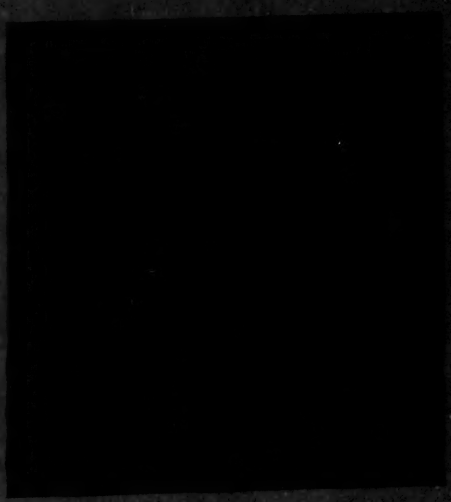

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THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

AUGUST, 1950

COMMUNICATIONS

THE WATER-DRINKING TEST*†

BY

WOLFGANG LEYDHECKER

From the Institute of Ophthalmology, University of London. Director of Research, Sir Stewart Duke-Elder

THIS paper is a contribution to the study of the mechanism of the water-drinking test, attempting to answer the question whether it is a test for the function of the capillary endothelium, as the first investigators of this test assumed, or whether the osmotic changes of the blood account for the rise of the ocular tension. The first conception implies that chronic simple glaucoma is a general disease caused by dysfunction of the capillary endothelium. The second theory suggests that the defect lies in the eye itself. Each opinion has been strongly advocated by a clinic, the first at Bonn, the second at Heidelberg. Since an understanding of the arguments in the controversy may help to assess the present investigation, a short review of the literature follows.

* Received for publication February 1, 1950.

† The expenses of this research were defrayed by the Alexander Pigott Wernher Memorial Trust.

Literature

Experiments at Bonn.—Marx (1925; 1926 a, b, c, d; 1928), working at the Medical Clinic at Bonn, investigated the drinking test (1 litre water within a few minutes in a state of fasting). The haemoglobin percentage of the blood was measured every 15 minutes and the volume and specific gravity of the urine every 30 minutes. In normal cases the haemoglobin curve showed a dilution of the blood with a peak between 20 and 40 minutes, and a smaller maximum between 50 and 80 minutes. The original level was regained in 4 to 5 hours. Identical curves were obtained after drinking 1,000 cc., 250 cc., or 50 cc. water or normal saline. The diuresis was less constant. The specific gravity showed one phase of dilution only. Abnormal reactions, found in diseases of kidney and heart or in glandular insufficiency, were attributed to a general disturbance of the capillary endothelium, which was regarded as the barrier to the exchange between blood and tissue.

Schmidt, also at Bonn, took the interpretation of this test for granted and reported on sixteen cases of chronic simple glaucoma in which only these systemic responses were studied (Schmidt, 1928a). The ocular tension was not measured. Eight of the sixteen haemoglobin curves were abnormal, but in his opinion fifteen patients reacted abnormally because of delayed diuresis and/or irregular dilution of the urine. His conclusion was that in chronic simple glaucoma a disturbance of the capillary endothelium is present.

In later publications (1928b, c; 1929; 1931) he also reported a rise of the ocular tension during the test in all cases of untreated simple glaucoma, which was the same after drinking 1,000 cc., 250 cc., 50 cc., or 20 cc. water (1931). This is his only valid argument against an osmotic basis for the drinking test, his others being erroneous, *e.g.*, when he pointed out that hydraemia produced by heat or by the injection of hypertonic solutions did not produce a rise of the intra-ocular pressure (1928c).

His views were shared by his teacher Römer (1928) and his coworker de Decker (1929a, b) who applied the water test in seventeen cases of retinal detachment and obtained a significant rise of tension in seven of them. This disease, too, was therefore attributed by de Decker and by Römer to a disturbance of the intra-ocular capillaries.

Although in a control test with normal saline de Decker obtained smaller rises, which were within the error of tonometry (the report on a second case is misleading), he attributed the effect to the increase of plasma in the blood (1929b).

Criticism from the Eye Clinic at Heidelberg.—Serr (1928) argued in the discussion following Schmidt's paper that the osmotic hypotonia of the blood was sufficient to explain the rise of the intra-ocular pressure in glaucoma. A normal eye can compensate the inflow of liquid by an increased outflow of aqueous, but not a glaucomatous eye. Lobeck (1930) from the same clinic, published a detailed criticism with essentially the same arguments. He did not, however, contribute any experiments of his own.

Further Application of the Test.—No further contribution has been made to our knowledge of the mechanism of the test. Later observers (Bloomfield and Kellermann, 1947; Evans, 1942; Heegaard and Larsen, 1931; Kronfeld, 1949; Majorova and Glinika, 1939; Ohm, 1936; Spadavecchia, 1936; Sugar, 1948; Tichomirov, 1940, 1941; Wegner, 1930a, b, c) have investigated mainly the clinical value of the drinking test, by considering the percentage of positive results of the tests in established glaucoma, or by comparing it with other tests. Animal experiments were contributed by Yudkin and Gilman (1933).

There is not complete agreement on the reaction of normal eyes, the usually accepted limit being a rise of 6 mm. Hg. Sugar (1948), however, regards even a rise of 9 mm. Hg, or a ceiling of 32 mm. Hg, as normal.

The test is mostly recommended for chronic simple or wide angle glaucoma (Kronfeld, 1949), but Sugar doubts whether it can not equally be applied in the narrow angle type. He combined it with the lability test of Bloomfield and Kellermann (1947), and then regarded rises of 10 mm. Hg, or a ceiling of 38 mm. Hg, as still normal. Negative tests in established wide-angle glaucoma were attributed by Kronfeld to an anomalous systemic response to the ingestion of water, but unfortunately no details of the systemic anomality in these cases were reported by him.

The Present Investigations

Terminology.—All patients had primary glaucoma. No eyes with merely suspected glaucoma or with any additional disease were included. The eyes are classified in two ways:

(1) according to the course of the disease into simple or congestive glaucoma. "Simple glaucoma" signifies the absence of any clinical signs of congestion or history of previous congestive attacks; in the presence of either of these the case is classified as "congestive glaucoma".

(2) In most eyes gonioscopy by means of the Goldmann contact lens and the Haag-Streit slit-lamp was performed. These eyes are classified into wide-angle or narrow-angle glaucoma, according to whether the ciliary body was visible or not.

Number of Patients.—There were altogether 42 patients; nineteen patients (34 eyes) in the simple glaucoma group and twenty-three patients (40 eyes) in the congestive glaucoma group.

Gonioscopy was done on 27 eyes of the simple glaucoma group and it was found that eight of them had a narrow and nineteen had a wide angle. When 29 eyes of the congestive glaucoma group were examined with the gonio-lens, eighteen had a narrow, and eleven a wide angle. It is noteworthy that so high a percentage of eyes with a wide angle occur in this group. Four of these eleven eyes had more than half of the angle occluded by peripheral anterior synechiae and all of them had a shallow anterior chamber of less than 2·5 mm.

Methods.—All patients had no miotics for at least 24 hours and had no breakfast in the morning before the test. They drank the water within 3 minutes on the average, the minimum time being 1 minute, the maximum 5 minutes. It is essential that this last time is not exceeded. A sandwich was given not earlier than half an hour after the ingestion of the water. Patients able to attend several times drank 1,000 cc. at the first visit, 500 cc. in several subsequent tests, then 250 cc. once, and, if all these tests were positive, once 500 cc. normal saline and finally 50 cc. water.

Tonometry.—This was performed by the author in all cases, using the Schiötz X-tonometer with the patient lying flat on his back. The illumination of the room was constant. Readings were taken half an hour before and again immediately before the test, care being taken to start the test neither in a rising nor in a falling spontaneous phase. From this rule 22 exceptions were made; this will be discussed later. A stop watch was started when the patient began to drink and the tonometry was repeated at 10-minute intervals, or more frequently, until the end of the first hour, and then half-hourly.

Urine.—This was collected in the present study before the test, then half-hourly during the next 3 hours; in some cases, however, the patients were available for only 2 hours.

Conductivity Tests.—For these blood was taken from the cubital vein before the test and 4 to 6 further samples between tonometric measurements. It is essential to collect the blood into absolutely dry syringes, needles, and glass tubes. In the first three cases exactly the same amount of heparin was added to each tube, so that after centrifuging, plasma was obtained. As fibrin disturbed the measurement of the conductivity by clotting on the electrodes, all further tests were done with serum only. The glass tubes were corked as soon as the blood was delivered into them, centrifuged, and kept in the refrigerator until the conductivity was tested some 3 hours later. To measure the conductivity the apparatus of Davson, Duke-Elder, and Maurice (1949)* was used.

Results of the Water-Drinking Test

Incidence of Positive Results.—One hundred and sixty-eight water drinking tests with 1,000 cc., 750 cc., 500 cc., and 250 cc. were done on altogether 74 eyes. Control tests with 50 cc. water or 500 cc. normal saline are not included in this number. A rise of the ocular tension of 6 mm. Hg and more, or from a normal tension below 30 mm. Hg to a pressure over 30 mm. Hg, was regarded as a positive result (+). A rise of more than 9 mm. Hg, or from a normal tension below 30 mm. Hg to a pressure over 32 mm. Hg, was regarded as strongly positive result (+ +). Details are given in Table I. The approximately equal incidence of positive tests in unoperative eyes with simple glaucoma (77 per cent.) and congestive glaucoma (74 per cent.) is striking. The same holds good when the classification is made into wide angle (positive 70 per cent.) and narrow angle (positive 69 per cent.) glaucoma. The

*I should like to thank these authors for their kind permission to use the apparatus.

high incidence of positive tests in operated eyes was in accordance with the post-operative history of these cases.

Strongly positive tests were obtained in 50 per cent. of the unoperated eyes (in simple glaucoma, eight out of 22; in congestive glaucoma, fourteen out of 23).

TABLE I

Incidence of Positive Tests

Number of eyes		Classification of eyes	Reactions + No.	Reactions + %	Reactions ++ No.	Reactions ++ %	Number of tests	
74		*Simple Glaucoma*						168
	22	unoperated ...	17	77	8	36	54	
	12	operated	5	41·5	4	33	25	
		Congestive Glaucoma						
	23	unoperated ...	17	74	14	61	55	
	17	operated	7	41	6	35	34	
56		*Wide angle*						151
	20	unoperated ...	14	70	7	35	55	
	10	operated	2	20	1	10	17	
		Narrow angle						
	16	unoperated ...	11	69	8	50	51	
	10	operated	6	60	2	20	28	

The incidence of positive tests is approximately the same in unoperated eyes with simple glaucoma as in congestive glaucoma. The width of the chamber angle is unimportant in assessing the result.

Dependence of the Rise of the Ocular Tension on the Amount of Ingested Water.—In the evaluation given above, all tests from 1000 cc. to 250 cc. water were included. For a comparison between 1000 cc. and 500 cc. tests it must be appreciated that in most patients only one test with 1000 cc. was done, but on the average four with 500 cc. were done. The incidence of positive (+) and of strongly positive (++) tests for each group is shown in Table II. No reference is made to the width of the chamber angle as it seemed of minor importance (see Table I). The number of eyes compared in this way is only 42 (fifteen operated and 27 unoperated), as some patients were not willing to attend several times. In the 27 non-operated eyes, positive results were obtained in 21 eyes with 1000 cc. water, and in fifteen eyes with 500 cc. water. In eleven out of the 27 eyes, the increase of tension with a 500 cc. test was slightly greater than with a 1000 cc. test.

The explanation lies in the great variability of the rise of tension

in the same eye after the ingestion of water. For example, in repeated 500 cc. tests the same eye may show a rise of 2, 9, or 12 mm. Hg (patient No. 28 right eye), of 7, 16, or 20 mm. Hg (patient No. 28 left eye), of 7, 11, or 14 mm. Hg (patient No.

TABLE II

Comparative Tests with 1,000 *cc. and* 500 *cc. Water in Identical Eyes*

Number of eyes	Classification of eyes	Reactions			
		+		++	
		1,000 cc.	500 cc.	1,000 cc.	500 cc.
	Simple Glaucoma				
14	unoperated	10	5	3	2
6	operated	5	3	4	1
	Congestive Glaucoma				
13	unoperated	11	10	9	8
9	operated	4	3	1	1

The incidence of positive tests is slightly smaller after the ingestion of 500 cc. water than after 1,000 cc. No strongly positive tests were obtained in these eyes with 250 cc. tests. The ingestion of 50 cc. water never resulted in any alteration of the ocular tension.

73). Both eyes tend to react similarly. Thus the rise of 2 mm. Hg in the right eye of the first patient quoted above (No. 28), was coincident with the comparable low rise of 7 mm. Hg in the fellow eye. Anticipating results which will be discussed later it may be mentioned here that this variability is not caused by differences in diuresis, but either by different systemic reactions (quicker or slower restoration of the osmotic pressure of the serum) or by the interference from the spontaneous phases of the ocular tension (the nature of which is as yet little understood but is probably vasomotor) or by both. As has been pointed out, one must also take into account that in most cases only one 1000 cc. test was compared with several 500 cc. tests, among which the test which gave the highest rise of tension was taken for comparison.

Nevertheless, the rise of tension and the incidence of positive tests was clearly greater with 1000 cc. than with 500 cc. The influence on the result of the test of the amount of water drunk is further demonstrated by the fact that in no case did the test with 250 cc. give a rise of tension as high in the same eye as did the test with 1000 cc. No 250 cc. test was strongly positive.

As for the clinical application of the test, which will be discussed at the end of this paper, we may conclude that at least two tests are required before the result can be regarded as negative.

The Curve of the Ocular Tension.—The ocular tension begins to rise in typical positive cases 5 to 10 minutes after the start of the drinking and reaches a peak in 20 to 35 minutes (Figs 1 and 2). Usually it maintains its maximum value not longer than 10 minutes and subsequently begins to fall to the original level or, more frequently, below it. Atypical curves may show a primary fall of the tension (Fig. 3 (*a*)). It seems improbable that this is

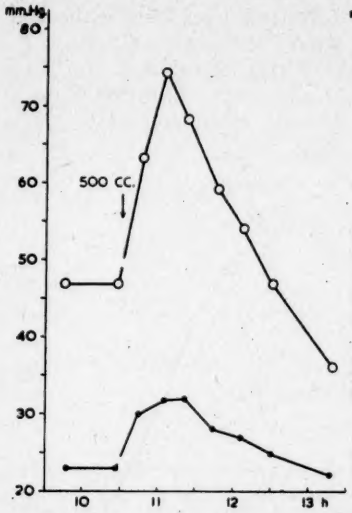

FIG. 1.—R.E. chronic congestive glaucoma. L.E. subacute congestive glaucoma. Neither eye had been operated on. Typical curves.

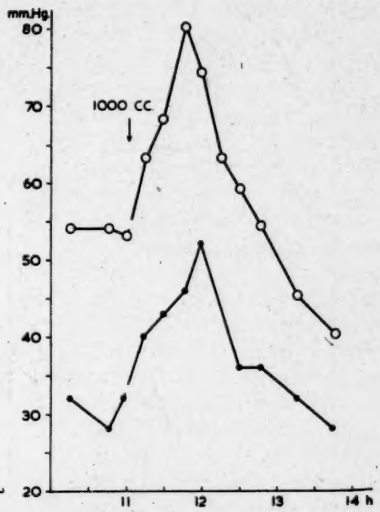

FIG. 2.—Both eyes chronic congestive glaucoma, not operated on. Typical curves.

In all graphs the tension curve of the right eye is drawn in dots, and that of the left eye in circles. A break in the curves below the arrow signifies the ingestion of water.

a result of massage during the tonometry, as repeated tonometry on other occasions never produced a fall of tension of the same order in these eyes. It presumably occurred, in the present example, during a spontaneous rising phase which also makes a massage effect improbable (Thomassen, 1946). Fig. 3(*a*) also shows that the tension remained at its maximum longer than indicated above, and fell only after pilocarpine treatment. This was likewise observed in some other patients. The phenomenon is not

associated with any particular structure of the eye, as Fig. 3(*b*) shows, which is a perfectly typical curve of the same patient obtained on a different day. It is also not due to an abnormal systemic reaction, as is shown by the conductivity curve of the serum in Fig. 3(*a*), which will be discussed later, together with a further atypical feature —a second (late) rise of tension.

Normal eyes have either no rise of tension at all (Fig. 4), or a rise less than 6 mm. Hg at the same time as glaucomatous eyes have their peak (Fig. 6).

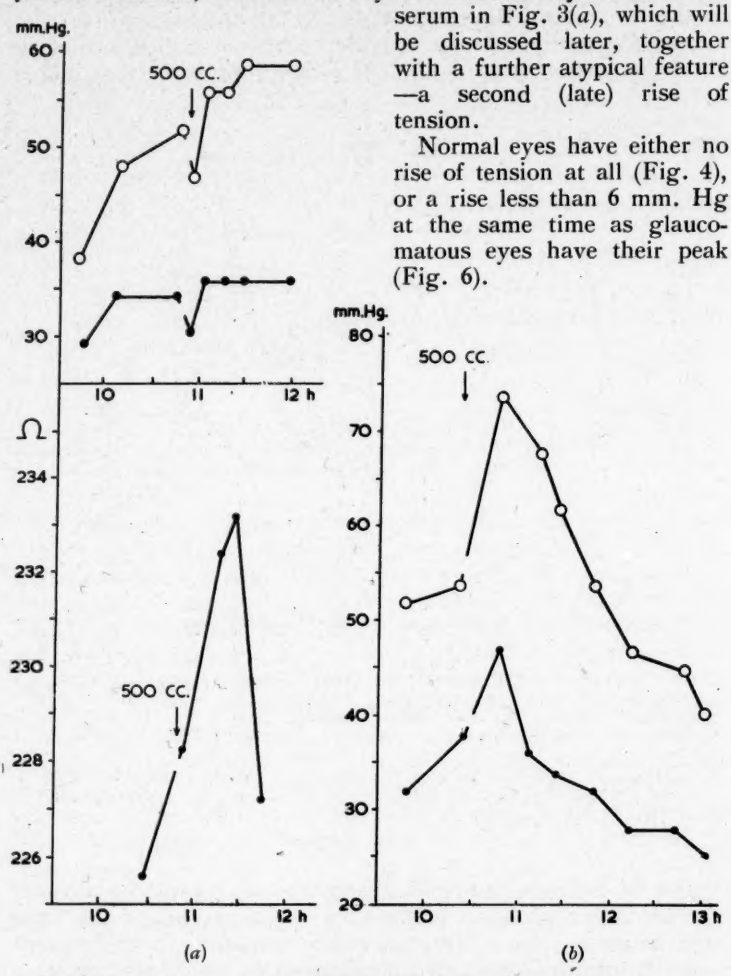

FIG. 3.—Both eyes chronic congestive glaucoma, not operated on. Atypical tension curves in Fig. 3*a* (primary fall of tension; the maximum is held for more than 30 minutes). The conductivity curve in Fig. 3*a* below the tension curves is normal. On another day typical tension curves were obtained (Fig. 3*b*).

The Mechanism of the Water-Drinking Test

Diuresis.—There is general agreement that a normal individual discharges all the water ingested in a drinking test within four hours, and that most of the urine is produced within the second and third hour (Domarus, 1942). During the two days preceding the test the patient should eat dry food and have a limited quantity of fluid only. Unfortunately this restriction could not be kept by the out-patients concerned in this report, and in most cases it was not possible to keep them under observation for four hours. It seems, however, reasonable to regard a diuresis of more than nine-tenths of the ingested water within the first two hours, or of more than the total amount within three hours, as high. On the other hand a diuresis of less than six-tenths within the first two hours, or less than eight-tenths within three hours, is taken as insufficient in the following evaluation.

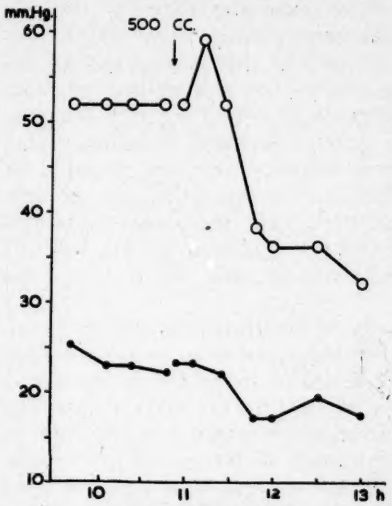

FIG. 4.—R.E. normal, L.E. acute congestive glaucoma, trephined and cyclodialysis. No rise of tension in the normal eye. Fall below the original level after positive test in L.E. The tension of the normal eye falls simultaneously.

In the group of simple glaucoma, 29 water tests with control of the urine were done on eighteen patients. Five of the tests showed a delayed (insufficient) diuresis, fifteen a high, and only nine were between the limits mentioned above.

In the group of congestive glaucoma, 38 water drinking tests with control of the urine were done on 22 patients. In seven of the tests the diuresis was delayed, in twenty it was high, and eleven cases were between these two groups. None of the patients suffered from diseases of kidney or heart.

Details regarding the cases which showed delayed diuresis are of interest, as it might be suggested that the retention of water in the body affects the ocular tension by favouring an oedema, regarded by Magitot (1929a, b) as the essence of glaucoma. From Table III it will be seen that there is no correlation between the rise of the tension and delayed diuresis. It occurred in twelve

tests (19 eyes) but only in five tests was a rise of more than 9 mm. Hg recorded, while in five other tests the rise was less than 6 mm. Hg. Furthermore, in three patients (Nos. 65, 64, and 60) showing a subnormal diuresis, the rise of the ocular tension was greater when a repeated test gave a medium or high diuresis.

In two subjects (Nos. 62 and 45) the reverse happened, and in one patient (No. 25) the rise of tension was the same whether the diuresis was high or delayed.

It will also be seen from these examples that the diuresis may differ from day to day in the same person. Five out of forty patients (Nos. 25, 45, 60, 64, and 85) in this survey had at one time a delayed diuresis and at another test a high diuresis, and two other patients alternated between high and medium diuresis. These observations indicate a great individual variation. One reason for this may be that these subjects were not prepared on the two days preceeding the test with a controlled diet as were the hospitalized patients. Nevertheless the individual variations of diuresis are greater than could be explained in this way, as there was no reason to suppose that the same patient varied his diet to a large extent.

The curve of the specific gravity of the urine, the other criterion of the systemic response to the drinking test, was normal in all but two cases; *i.e.*, it showed a concentrated urine before the test, a dilution up to a specific gravity of 1000 for the main volumes of the urine, and a gradual concentration towards the end of the test.

The diuresis following the ingestion of 500 cc. normal saline was much smaller than after 500 cc. water. This has also been described by Marx (1926c, 1928). In six cases the average within the first two hours was 125 cc. The seventh patient (No. 85) had the exceptionally high amount of 280 cc. urine in two hours, as compared with his very poor diuresis of 190 cc. in two hours after 1000 cc. water. His dilution curve was abnormal. None of the seven patients had a rise of tension with the 500 cc. normal saline test.

Summarizing briefly, in 65 out of 67 tests the dilution curve of the urine was normal, but the diuresis was delayed in twelve tests. The high incidence of insufficient diuresis and the great variability in many patients points to a systemic disturbance associated with glaucoma, though it must be admitted that insufficient controls in healthy subjects have been done. Quick diuresis was not taken as being abnormal, because it was found by other observers (Verney, 1929) in healthy subjects.

It must be emphasized, however, that delayed or high diuresis did not coincide with either a high or a low rise of the ocular

TABLE III

Subnormal Diuresis and Rise of the Ocular Tension

Patient's Number	Type of Glaucoma	Quantity of Water (cc.)	Rise of Tension (mm. Hg Schiötz)		Diuresis (cc.)	
			RE	RE	2 hrs.	3 hrs.
83	Simple unoperated	1,000	+ 9(43/52)	+16(52/68)	*190*	*450*
63	Simple unoperated	1,000	+ 6(19/25)	+ 6(19/25)	*510*	*590*
		500	0(28)	+ 6(28/34)	*90*	*210*
60	RE simple unoperated	1,000	+ 5(54/59)	+11(36/47)	*510*	*810*
	LE simple operated	500	+11(63/74)	+14(38/52)	540	640
25	LE simple unoperated	1,000		+ 5(28/33)	1,000	1,130
		1,000		+ 6(32/38)	*320*	860
77	LE congestive unoperated	1,000		+ 7(27/34)	*530*	—
5	RE congestive unoperated	1,000	+ 4(18/22)		*480*	—
101	RE congestive operated	1,000	+10(37/47)	+23(45/68)	*490*	—
	LE congestive unoperated					
62	Congestive operated	1,000	+ 4(34/38)	+ 2(36/38)	690	—
		500	+ 8(32/40)	+ 6(39/45)	*280*	—
64	Congestive operated	1,000	+ 2(23/25)	0(32)	*240*	*360*
		500	+ 4(21/25)	+ 4(23/27)	520	630
45	Congestive operated	1,000	+ 6(30/36)	+ 9(36/45)	*510*	*560*
		500	+ 4(30/34)	+ 3(40/43)	500	610
65	Congestive operated	1,000	+ 7(25/32)	+20(54/74)	*300*	*390*
		500	+ 9(23/32)	+27(47/74)	420	500

Eleven patients with subnormal diuresis (in italics).

The numbers in brackets give the ocular tension before the test and at its maximum. There is no correlation between the rise of the ocular tension and the rate of diuresis. For comparison, tests with medium or quick diuresis in the same patients are given in normal print.

tension. Apparently, therefore, the diuresis and the rise of the ocular tension must be considered independent and cannot be brought into causal connection.

The Conductivity of the Serum.—The blood serum in all the cases tested showed an increase of electrical resistance. In 21 cases enough, *i.e.*, from four to six, samples of blood were taken to construct a curve. Two typical examples are given in Figs 5 and 6.

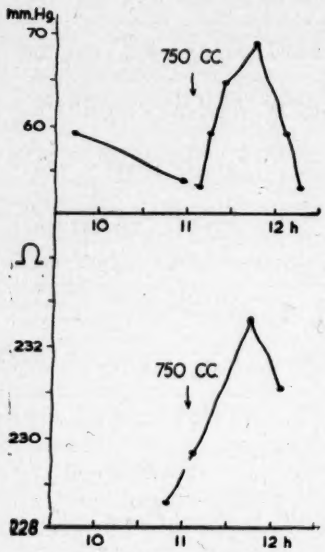

FIG. 5.—*Both eyes simple glaucoma, not operated on. The tension of the L.E. was over 80 mm. Hg. Tension curve and conductivity curve, in a general sense, run parallel.*

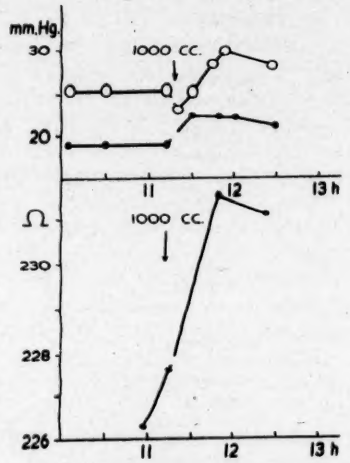

FIG. 6.—R. E. simple glaucoma, trephined. L.E. normal. The tension in the R.E. which is filtering well, *does not alter significantly.* The normal L.E. shows a rise of tension within normal limits simultaneously *with the increase of resistance in the* blood serum; the subsequent fall is almost parallel in both curves.

They show that in a general sense the tension and resistance curves run parallel, and that the maximum of the resistance *coincides with that of the ocular tension.* In other curves (Fig. 7(*b*)) the former preceded the latter by a few minutes. The resistance curve had a similar shape in all cases, whether the ocular tension rose significantly (Fig. 5), slightly (Figs 6, 8(*a*), and 8(*b*)) *or not at all (Fig. 7(a)).* The maximum occurred at any time between 5 and 38 minutes after the start of the drinking. It *appeared that the peak was earlier after* the ingestion of 500 cc.

than after 1000 cc. water, and earlier after quick drinking than after slow drinking.

The rise of the resistance was not the same in different subjects, and even in the same subject (Figs 8(*a*) and (*b*)) when the test was repeated with the same amount of water. When the effects of a 1000 cc. test and a 500 cc. test in the same patient, were compared it was found that the rise of resistance was larger after the greater volume of water (Figs 7(*a*) and (*b*)). The ocular tension did not change at all in the 1000 cc. test, and was within the normal limits (R.E. + 3 mm. Hg, L.E. + 4 mm. Hg) in the 500 cc. tests. Figs 7(*a*) and (*b*) and Figs 8(*a*) and (*b*) show that the time of the maximum varies for the same subject.

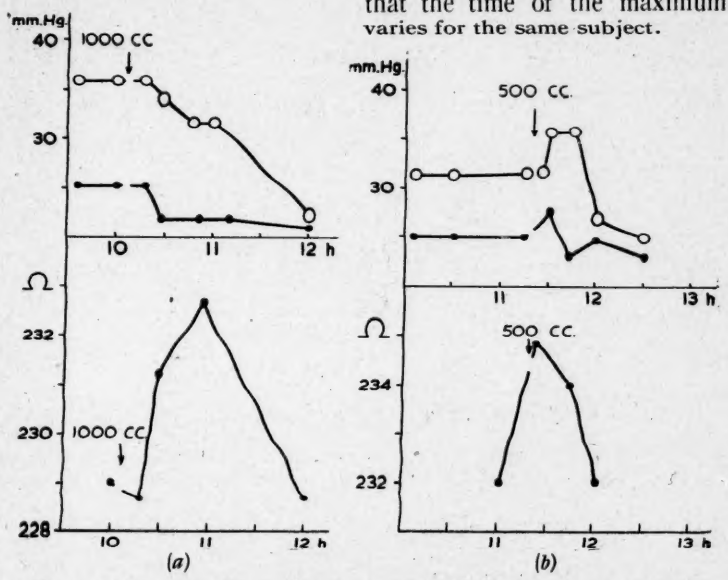

FIG. 7.—R.E. normal, L.E. chronic congestive glaucoma. not operated on. Figs 7*a* and 7*b* both show negative tests. The increase of resistance of the serum is greater after the ingestion of 1,000 cc. water than after 500 cc. The peak of this curve occurs after 37 minutes in the first case and after 5 minutes in the second.

Although some patients showed a greater increase of resistance after 500 cc. water (the maximum increase being 7·7 ohms) than others had after 1000 cc. (the minimum increase being 3·5 ohms), the average rise after 500 cc. water was significantly lower than after 1000 cc. Twelve curves were obtained in the 500 cc. tests with an average rise in resistance of 3·45 ohms. Four 750 cc. tests gave an average of 3·6 ohms, and four 1000 cc. tests an average of 4·8 ohms.

An increase of electrical resistance means that there is a decrease in the number of ions present in a given volume of serum. It is

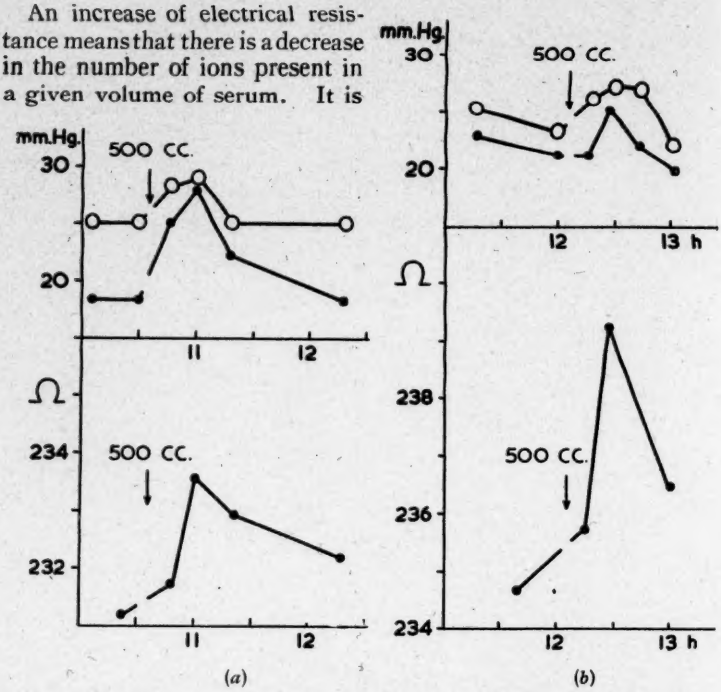

FIG. 8.—Both eyes chronic congestive glaucoma, trephined. The tension curves in Figs 8*a* and 8*b* are both normal. The resistance curves are of different heights, though the quantity of ingested water was the same in both cases. The peak occurs after 30 minutes in Fig. 8*a* and after 39 minutes in Fig. 8*b*.

unlikely that a fraction of the ions of the normal serum suddenly disappears. The only explanation is that undissociated fluid has been added to the serum in these tests, namely, water absorbed from the intestines. The absorption is a physiological, not a purely physical, process, which will differ in rate and degree in each subject. Subsequent attempts of the body to re-establish osmotic equilibrium by a flow of water from the blood into the tissues will show even greater individual variations. In an eye where the outflow of aqueous is hampered this would lead to a rise of tension simultaneously with, or little later than, the osmotic changes in the blood. The close correlation between the resistance-curve of the serum and the tension curve of the eye confirms this reasoning, and we may conclude that *the osmotic*

changes of the blood cause the rise of the ocular tension in the water-drinking test.

When the initial tonicity of the serum is re-established the outflow of aqueous is augmented by osmotic forces, the aqueous humour now being relatively hypotonic, and indeed in most cases the ocular tension falls soon afterwards, frequently below the original level (Figs 1, 2, 3(*b*), 4, 7(*a*) and (*b*)). There are, however exceptions of two types.

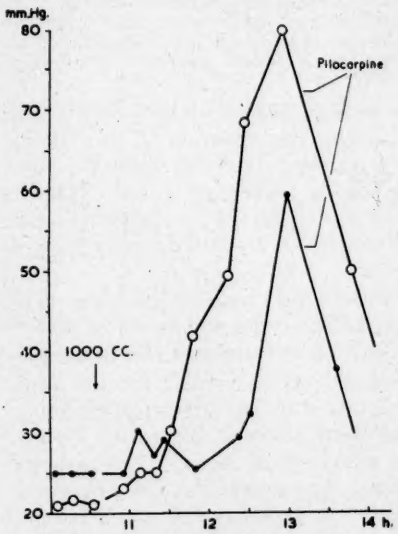

FIG. 9.—Both eyes chronic congestive glaucoma, not operated on. After the primary rise, due to the ingestion of water, a late second rise occurs. Compare Fig. 10.

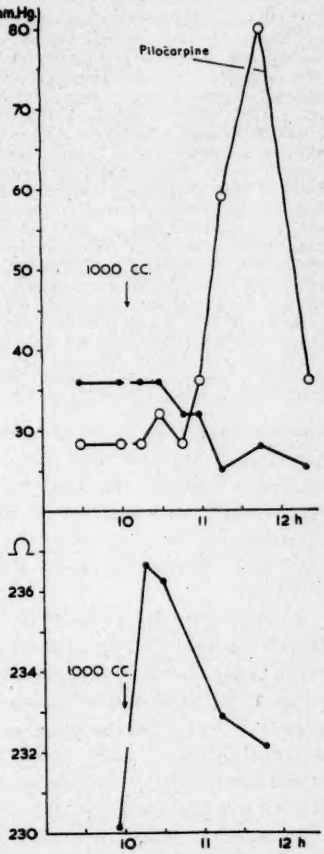

FIG. 10.—Both eyes chronic congestive glaucoma. R.E. trephined, L.E. not operated on. The resistance curve of the serum shows that the late second rise of the ocular tension is not due to osmotic effects.

(*a*) The ocular tension remains for more than 10 minutes at the high level attained at the end of the rise. Fig. 3(*a*) is an example of this; the cause of this irregularity cannot be anatomical, since in another test (Fig. 3(*b*)) a typical curve was given by the same eyes. The curve of the conductivity of the serum in

Fig. 3(*a*) shows that this cannot determine the anomalous reaction in this case. The only alternative explanation seems to be that variations of the ocular tension of a vasomotor nature interfered with the osmotic changes of tension. This influence will be discussed later.

(*b*) The ocular tension rises continuously until it is stopped by miotics (Fig. 9), or, after the primary rise at the usual time (20-35 minutes) it shows a late second rise which continues if untreated (Fig. 10). Fig. 9 shows that the left eye reacted to the drinking test with a relatively small rise within the first 40 minutes, remained at the new level for 10 minutes, and subsequently rose steadily from 25 to 80 mm. Hg. The right eye showed a primary typical rise, and a somewhat atypical fall, and then accompanied the left eye in its rise, until both eyes were given intensive pilocarpine treatment which reduced the tension to a normal level. No subjective symptoms were associated with these changes of tension. This puzzling incident was first attributed to the drinking test itself. Luckily, however, in a second case (Fig. 10) blood samples had been taken before the test and 15 and 30 minutes after drinking. When now, after a primary rise and a subsequent regular fall in the tension of the left (unoperated) eye, a new rise of tension was observed, further blood samples were taken. The conductivity-curve makes it evident that *the second rise is not of osmotic nature,* since it happened simultaneously with the re-establishment of the original osmotic pressure of the blood. Both patients suffered from congestive glaucoma. The patient of Fig. 10 was seen several times later with a spontaneous tension of 70 to 80 mm. Hg in the left eye, although she had taken miotics a few hours previously. Each time intensive pilocarpine treatment normalized her tension. She was returned to her surgeon.

Control Tests with Normal Saline or 50 cc. Water.—It has been shown above that the result of the drinking test depends on the volume of water ingested in, though the variability of physiological regulation may obscure the evidence in individual cases. This is contrary to the findings of Schmidt (1931) who claimed that he obtained exactly the same result with 50 or 20 cc. water as with 1000 cc.

Drinking tests with 50 cc. were done therefore on eight eyes, which had reacted in numerous 500 cc. tests with rises of 8 to 19 mm. Hg. None of these eyes showed the slightest rise of tension.

As a further confirmation of the osmotic basis for the water drinking tests, twelve eyes were tested by the ingestion of 500 cc. normal saline. They too had been selected according to their reactions to 500 cc. water, after which all of them had consistently shown a significant rise of tension. In no case was a rise observed. The small diuresis following this test in six out of seven patients has been described above.

Lack of Evidence for the Action of a Vasomotor Factor.—Thomassen and Leydhecker (1950) have shown that the lability test of Bloomfield and Kellermann (1947) presumably changes the blood volume in the eye and gives positive or negative results according to whether the ocular tension is in a rising or in a falling spontaneous phase. That the same holds good for the venous congestion test, will be shown in another paper.

The influence of spontaneous phases in the tension of the eye on

the result of the test cannot be directly assessed, as the measurement of the phase is made impossible by the changes of tension caused by the test itself. It is, however, possible to determine whether the tension is rising or falling before the beginning of the test and to indicate whether this has any influence on the result.

Fifteen eyes were tested when the tension had fallen 3 to 14 mm. Hg, and seven eyes after the tension had increased 4 to 8 mm. Hg in the preceding 30 minutes. The spontaneous alterations of tension seem to have no decisive influence on the test, but the curves of the drinking test were perhaps modified by them. An example is given in Figs 11(*a*) to (*c*), representing curves from the same patient. The 1000 cc. test (Fig. 11(*a*)) was strongly positive, although it was started after a fall of 5 mm. Hg in the right eye, and of 14 mm. Hg in the left eye, during the 30 minutes preceding the test. The first 500 cc. test (Fig. 11(*b*)) was started after a fall of tension of both eyes and gave a small rise only, whilst greater rises were obtained when the tension had been constant previously (Fig. 11(*c*)).

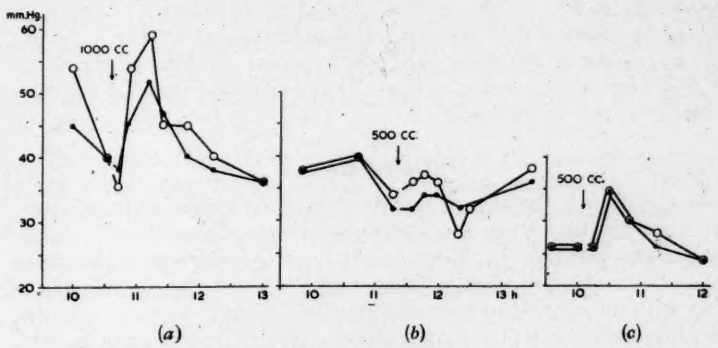

FIG. 11.—Both eyes chronic glaucoma, trephined. See text.

It must be emphasized, however, that this influence of variations of tension on the drinking test is proved to be unimportant by Fig. 11(*a*), and that there is no evidence that the differences between Figs 11(*b*) and 11(*c*) were caused in the way suggested. Similar variations of the rise of tension occurred without any preceding changes of tension in the same eye after the ingestion of the same volume of water.

Irregular curves, as in Fig. 12, cannot be explained by osmotic changes and interference by vascular causes must be postulated.

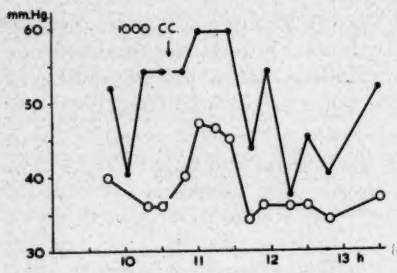

FIG. 12.—Both eyes simple chronic glaucoma. R.E. not operated on, L.E., iridencleisis. The irregular curve of the R.E. is probably due to vasomotor influences.

In approximately forty tests a sphygmomanometer-cuff was put around the neck of the patient during the rise and during the fall of the tension in the drinking test, and inflated to 45 mm. Hg for one minute. Though all these venous-congestion tests were done in a definite phase of ocular tension, and were therefore all expected to be positive* in an increasing and negative in a decreasing phase, it was found that this test was as frequently negative as positive in any phase of the drinking test. Since the venous-congestion test works by an alteration of the blood volume of the eye, and since it may be supposed that the spontaneous phases are also caused by vasomotor changes, it can be concluded that *the phases brought about by the drinking test have little if anything to do with vasomotor alterations of the intra-ocular vessels and that hence they are fundamentally different from spontaneous phases.*

Discussion

It was found that the water-drinking test gives approximately the same results in non-operated eyes suffering from chronic simple glaucoma (positive in 77 per cent.) as in congestive glaucoma (positive in 74 per cent.). The width of the chamber angle is also without significance to the results. Repeated tests with the same quantity of water gave different results in the same patient, but variations in the amount of ingested water (50, 250, 500, and 1000 cc.) resulted in rises of ocular tension differing so considerably that there can be no doubt of the importance of this factor.

The resistance of the serum increased simultaneously with, or shortly before, the ocular tension in positive tests, and its increase depended upon the amount of water ingested. The shape and size of the conductivity-curves were about the same whether the ocular tension increased or not. In spite of the frequency of delayed or rapid diuresis no correlation was found between this and the reaction of the ocular tension. Neither was evidence

* Increase of ocular tension of more than 7 mm. Hg after one minute.

obtained that spontaneous, presumably vasomotor, phases are of any importance in determining the rise of tension. They influence the tension-curve only after the maximum is reached.

From these facts it can be concluded that the rise of tension in the drinking test is caused by changes in the osmotic pressure of the blood. Since these changes are the same in both positive and negative tests, normally and negatively reacting glaucomatous eyes must differ from positively reacting eyes either because the inflow of water is not increased when the blood serum becomes relatively hypotonic, or because an increased volume of aqueous can flow out more easily. The former mechanism is improbable according to the results of Kinsey, Grant, and Cogan (1942). Even if the decisive factor determining positive or negative tests is localized in the eye itself, this does not mean, that systemic reactions are unimportant in influencing the result. The degree and rate of the development of hypotonicity in the blood varies considerably in different people, and at different times in the same person. These differences are presumably caused by a varying rate of absorption and of the subsequent exchange of fluids between blood and tissue, which again depends on the amount of liquid taken by the patient on the days before the test, and on his individual regulation of the water exchange. Whether this regulation is hormonal or an autonomous function of the capillary endothelium is a question that must be answered by general physiology.

The mechanism of the water-drinking test as described above, throws new light on de Decker's experiments (1929b). In most cases of retinal detachment subretinal fluid is formed, which will become isotonic with the aqueous humour. When the blood is made relatively hypotonic, the volume of the subretinal fluid will increase, and subsequently the ocular tension rises.

The combination of the water-drinking test with a test altering the hydrostatic blood pressure and/or the amount of blood in the eye, as suggested by Sugar, offers no advantages. Thereby, two fundamentally different provocative tests are mixed, and one can not be sure which factor determines the result. Further research on provocative tests should, on the contrary, attempt to elucidate the mechanism of each test separately with the eventual aim of determining which function of the eye is defective in an individual case. On such a basis it would then be possible to combine tests for the same function or structure. With this knowledge negative tests would also be useful to indicate whether the tested function or structure is normal in a particular case, whereas, with our present knowledge they indicate nothing. It is probable that the

results of such investigations would contribute considerably to our understanding of the causes of primary glaucoma.

Clinical Application

The test gives approximately the same incidence of positive results in all types of primary glaucoma (69-77 per cent. with the 1000 cc. test). It should be applied clinically as follows:

Any treatment with miotics is stopped at least 24 hours before, exceptions being made only in severe cases, who have a rise of tension shortly after miotics are stopped. The tension is taken 30 minutes before and immediately before the test, in order to exclude as far as possible the risk of spontaneous rise of tension being mistaken for a positive result. The patient then drinks 1,000 cc. water in 5 minutes. This should not present anv difficulty to the patient. The tension is taken at exactly 15, 25, 35, and 50 minutes after the start of drinking. If this test is negative (rise of less than 6 mm. Hg), a second test with 1,000 cc. is done on another day. If this is again negative, it will not be necessary to repeat this test within 6 months. The tests should be done with 500 cc. water only with patients who find it impossible to drink 1,000 cc. in a few minutes. The incidence of positive results will be smaller with this method.

A final word for the immediate benefit of all glaucomatous patients. The ophthalmologist who is consulted in a case of glaucoma should warn his patient (very sternly) not to drink tea in bed before breakfast as many people do in this country. Two large cups of tea contain approximately 500 cc. liquid. Some of the patients of this paper reacted to this with rises up to 80 mm. Hg Schiötz.

Summary

(1) 168 drinking tests with 250 to 1000 cc. water were done on 74 eyes, 55 of which had not been operated on. A rise of 6 mm. Hg Schiötz and more, or from less than 30 mm. Hg Schiötz to a value above this figure, was regarded as a positive test. A rise of more than 9 mm. Hg Schiötz, or from a tension below 30 mm. Hg Schiötz to more than 32 mm. Hg Schiötz, was taken as a strongly positive test.

It has been shown for the first time that in unoperated eyes the incidence of positive tests is about the same in chronic simple glaucoma (77 per cent.) as in congestive glaucoma (74 per cent.). The width of the chamber angle is unimportant, positive tests occurring in unoperated eyes with a wide angle in 70 per cent., and in unoperated eyes with a narrow angle in 69 per cent.

The incidence of strongly positive tests in the same unoperated eyes was 36 per cent. in simple glaucoma, 61 per cent. in congestive glaucoma, 35 per cent. in wide angle glaucoma, 50 per cent. in narrow angle glaucoma (Table I). The typical

glaucomatous tension curve is monophasic with the peak between 20 and 35 minutes after the patient begins to drink. There is frequently a subsequent fall below the original level.

(2) When the result of tests with 500 cc. and with 1,000 cc. on the same eyes are compared, positive tests are found to be more frequent with 1,000 cc. than with 500 cc.

In unoperated eyes compared in this way, there were positive results with 1,000 cc. in 79 per cent., with 500 cc. in 55 per cent., and strongly positive results with 1,000 cc. in 44 per cent., with 500 cc. in 37 per cent. (Table II).

(3) No strongly positive results were obtained with 250 cc. The rise of tension was in all cases significantly lower than with 500 or 1,000 cc.

(4) Although the rise of tension clearly depends on the amount of water ingested, higher rises occurred in eleven eyes with 500 cc. than with 1,000 cc. [Only one 1,000 cc.-test, but numerous 500 cc.-tests were done on each of these eyes, and the 500 cc.-test which gave the highest rise of tension was taken for comparison.]

(5) There were great variations in repeated tests in the same eyes with the same volume of water. It has been shown that the different reactions of the ocular tension in the same eye is explained at least partially by variations of the physiological reactions following the ingestion of water, *i.e.*, the absorption and subsequent exchange of fluids between blood and tissue.

(6) The conductivity of the blood serum was measured during the drinking tests in 21 patients. It was found that the serum becomes hypotonic after the ingestion of water. The maximum hypotonicity occurred at the same time, or slightly before, the maximum ocular tension. Because of the exact correspondence of the conductivity-curve of the serum and the tension-curve of the eye, and the lack of evidence for any other important factor, it is concluded that *osmotic changes of the blood serum* after absorption of water from the intestines *cause the subsequent rise of the ocular tension.*

(7) Since the conductivity-curves had a similar shape and height whether the ocular tension showed a rise or not, it is concluded that the *result of the test depends mainly on events in the eye itself.* In positive tests the *outflow of aqueous must be hampered.*

(8) The urine was collected in 67 drinking tests. A diuresis of more than nine-tenths of the ingested water within the first two hours, or of more than the total amount within three hours, was regarded as high. A diuresis of less than six-tenths within the first two hours, or of less than eight-tenths within three hours was regarded as subnormal. According to these criteria the

diuresis was delayed in twelve, medium in twenty and high in 35 tests. Seven out of forty patients showed gross variations in the diuresis on different days. As there is no reason to suppose that the patients changed their diet to a large extent, a high incidence of systemic anomalies must be concluded, if one accepts the standard proposed. There was, however, *no noticeable coincidence of any particular type of diuresis with a high or low rise of the ocular tension.* It must also be remembered that the bulk of the diuresis takes place in the second and third hours, whereas the ocular tension reaches its peak in the first 30 minutes.

In two out of 67 tests the dilution of the urine was abnormal in not forming the typical monophasic curve. No patient suffered from diseases of heart or kidney.

(9) There was *no evidence that vasomotor changes affected the result of the test.* Spontaneous variations of the intra-ocular pressure before the test were unimportant. The venous-congestion-test was just as frequently negative as it was positive in the rising phase of the water-drinking test. This shows that *this rising phase is of a different nature from spontaneous phasic alterations in tension,* the first being due to osmotic differences between serum and aqueous, and second presumably of a vasomotor nature.

(10) Control tests, with 500 cc. normal saline or 50 cc. water, on eyes which had always produced a significant rise of tension in numerous previous tests, resulted in no case in a rise of the ocular tension.

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PERMEABILITY OF THE BLOOD-AQUEOUS BARRIER TO FLUORESCEIN DURING THE WATER-DRINKING TEST IN GLAUCOMATOUS EYES*†

BY

WOLFGANG LEYDHECKER

From the Institute of Ophthalmology, University of London. Director of Research, Sir Stewart Duke-Elder

THE permeability of the blood-aqueous barrier to dyes has been studied by numerous observers, but it was not until Amsler and Huber (1946) developed the technique of the fluorescein test that such tests became of clinical value. Two ml. 10 per cent. sodium-fluorescein are injected intravenously and its appearance in the aqueous in a dark-room is observed by means of the slit-lamp, the beam of which then develops a greenish colour in the anterior chamber. The increasing concentration of fluorescein in the aqueous is measured by the decreasing intensity of light which is required to produce a perceptible colour.

This intensity is determined by the current through the lamp which is regulated by a resistance and measured by an ammeter. When the current is plotted against time, a curve is obtained which shows with sufficient exactness the permeability of the blood-aqueous barrier to fluorescein. The normal variations are represented on a chart by a broad band. The individual variations of the same normal subject are up to 0·8 amp. on different days, but always within this band (Haefeli, 1946). In glaucoma abnormally high curves have been described by Amsler and Huber.

In a previous paper (Leydhecker, 1950) I have reviewed the literature concerning the water-drinking test of Marx (1925-28) and Schmidt (1928-31), and have shown its mechanism to be a water flow into the eye as a result of the difference of osmotic pressure produced between blood and aqueous. In about 70 per cent. of all cases of primary glaucoma, a rise of the ocular tension results, which is significantly greater than in normal eyes. In the present paper the question whether the flow of water into the eye and the subsequent rise of tension are associated with an abnormally fast inflow of fluorescein is investigated.

Method

Patients with an established diagnosis of glaucoma, but no other general or ocular disease, drank 500 or 1,000 ml. water within 2 to 4 minutes in a state of fasting. Miotics were discontinued at least 24 hours previously. Two ml.

* Received for publication March 4, 1950.

† The expenses of this research were defrayed by the Alexander Pigott Wernher Memorial Trust.

sodium-fluorescein were injected into the cubital vein, in most cases 3 to 7 minutes after the patient had started the drinking, in some up to 15 minutes later. The apparatus used for the fluorescein test had been calibrated by Huber himself. The original method of Amsler and Huber was employed, with the exception that every few minutes the room was illuminated, during which time the investigator wore a pair of close-fitting dark goggles. Thus it was possible to record the effect of the water-drinking test alone, without possible interference from the mydriasis due to the darkness on the outflow of aqueous and the intra-ocular pressure.

The ocular tension was measured 30 minutes before, and immediately before, the ingestion of water, in some cases after 15 minutes, and in all cases after 25, 35, and 45 minutes. On another day a control fluorescein test and measurements of the tension were repeated by the same observer, without the drinking test being done.

Results

Altogether 39 tests were done on sixteen patients with bilateral primary glaucoma. There were 24 eyes which had not been operated on, thirteen of them suffering from chronic simple glaucoma, eleven of the chronic congestive type. Eight eyes had been operated on; three of these had chronic simple glaucoma, and five had chronic congestive glaucoma.

No significant difference between the fluorescein-curves obtained without drinking and those after the ingestion of water were found in any patient. The fluorescein-curves of the same eye were in some cases slightly higher during the first 10 minutes after drinking, in other cases, they were the same or slightly lower. The differences averaged 0·3 amp., and never exceeded 0·7 amp. They are therefore well within the range of the individual variations of normal eyes on different days.

There was also no significant difference between curves obtained after the ingestion of 500 ml. and those after 1,000 ml. water in the same patient, nor was there any obvious correlation between the rise of tension and the height of the fluorescein-curve. This is of special significance since in some drinking tests the rise of the ocular tension was as much as 23 mm. Hg while the fluorescein-curve was the same as that found in the same eye without the drinking test and with a normal tension.

The type of glaucoma was important only in so far as most eyes with the congestive type gave fluorescein-curves higher than those with simple glaucoma. These differences, however, were not sufficiently marked to permit of the differential diagnosis. All curves were abnormally high.

Discussion

The independence of the permeability of the blood-aqueous barrier to fluorescein from the movement of water across it,

suggests that conditions in the human eye are similar to those shown by Kinsey and his co-workers (1942) to exist in that of the rabbit, as far as the exchange of water is concerned. These authors found by the use of tracer substances that water moves into and out of the eye independently of ions of small size, such as Na, PO_4, or Cl. It will therefore not be surprising to find in the present experiments that the relatively large ions of fluorescein diffuse separately from water.

The different experimental conditions, however, justified the investigation of this question for the human eye. Kinsey and others (1942) did not change the osmotic equilibrium between blood and aqueous, and their experiments were performed on the normal eye of the rabbit. In one instance only, when they injected D_2O into the vitreous, did an increased ocular tension result, and then much longer times for the exchange of water between eye and blood were obtained than when the intra-ocular pressure was undisturbed. In the present investigation the ocular tension was 32 to 54 mm. Hg before the ingestion of water in 33 cases, but its value had no influence on the positive or negative result of the water-drinking test, or on the height or shape of the fluorescein curve.

These results also support the view which has been put forward in a previous paper (Leydhecker, 1950) that alterations in the vascular condition of the eye are not a decisive factor in determining the outcome of the drinking test, since it is to be supposed that such alterations would be associated with changes in the permeability of the blood-aqueous barrier.

Summary

Sixteen patients with primary glaucoma have been subjected to a combination of the water-drinking test of Marx (1925-28) and Schmidt (1928-31) with the fluorescein test of Amsler and Huber (1946). It was found that the permeability of the blood-aqueous barrier of any one eye to fluorescein did not depend significantly on whether the tension rose after the ingestion of water or not, or whether the injection of fluorescein was made immediately after drinking, or up to 15 minutes later. The significance of these observations is discussed.

It is suggested that in fluorescein tests in glaucoma the room should be illuminated between each reading to prevent a possible interference of the mydriasis on the circulation of aqueous. A rise of the ocular tension due to this factor may otherwise be mistaken for a spontaneous phasic variation of the tension and

lead to erroneous conclusions. During these intervals the observer wears a pair of light-tight goggles.

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THE ARCUATE LENS OPACITIES OF MONGOLISM AND CATARACTS OF SIMILAR APPEARANCE *

BY

RONALD F. LOWE

Melbourne, Australia

IN 1934 Mann described six patients showing abnormalities of the iris and lens due to the persistence of capsulo-pupillary vessels. In some she actually demonstrated the persisting vessel, but more often it had atrophied after having produced the various deformities. There was always a gap or notch in either the ectodermal or the mesodermal part of the iris, sometimes in both, and evidences of persistent pupillary membrane were found either as tags from the lesser circle or as pigmented spots on the anterior lens capsule. In the lens there was usually a marginal notch and often an opacity localized to the region of the coloboma. Some of the opacities resembled small white arching bands within the lens (Fig. 1)†, while others were gross sector-shaped cataracts (Fig. 2)†.

Sometimes after facial blows a small arc of opaque fibres may be seen near the equator of a lens. The trauma may be indirect yet sufficient to disturb those cells dividing at the time. Clear fibres may be superimposed so that gradually the opacity becomes further from the surface. Slit-lamp examination much later in life allows the position of the opaque cells to be correlated with the size of the lens at the time of the injury (Fig. 5).

Another condition in which curved lens opacities are found is mongolism. During the examination of the lenses of 52 mongoloids previously reported (Lowe, 1949) I found eight with characteristic cataracts which I termed "arcuate opacities". Some of the mongoloid arcuate opacities presented appearances similar to those described by Mann (1934, 1938) but considerable differences were also evident.

The purpose of this paper is to extend the description of the mongoloid arcuate opacities. They are the most distinctive of the various types of cataract found in mongolism.

Arcuate Opacities in Mongolism

The simplest form of arcuate lens opacity shows as a small white splash deeply within the lens. Such a cataract can be seen

* Received for publication March 7, 1950.

† Figs 1 and 2 are reproduced from I. Mann (1937) "Developmental Abnormalities of the Eye". Cambridge University Press.

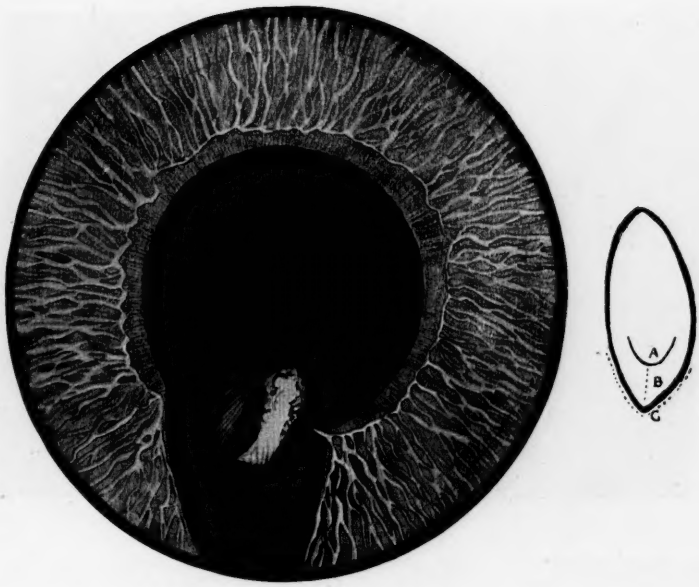


FIG. 1.—Curved lens opacity caused by persistence of a capsulo-pupillary vessel. Colobomata of the choroid, lens, suspensory ligament, and iris occur as associated defects (Mann).

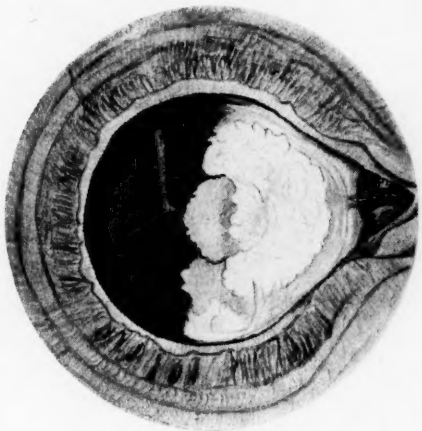
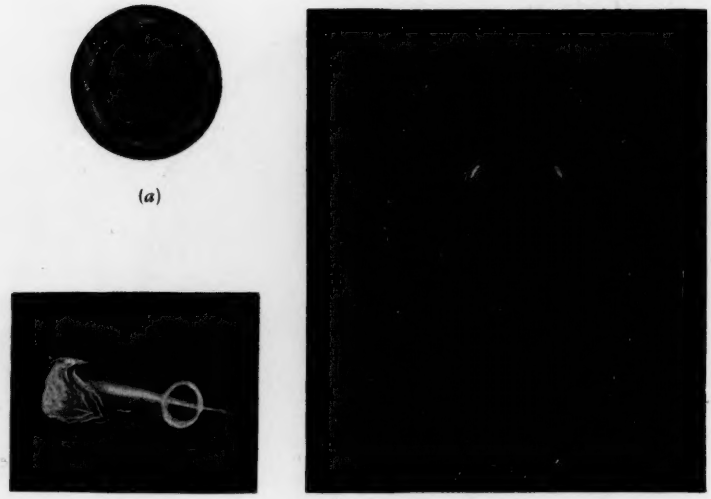
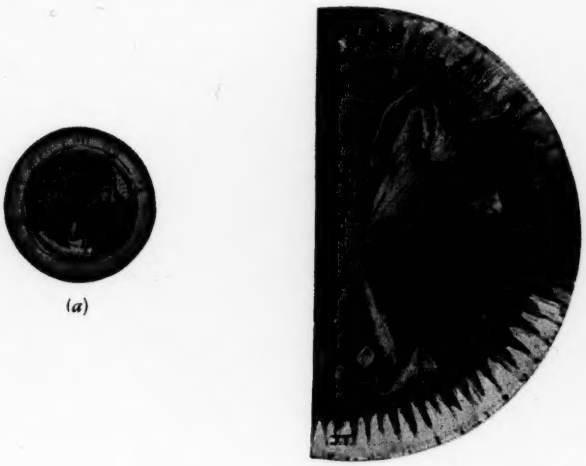


FIG. 2.—Large sector cataract caused by persistence of a capsulo-pupillary vessel, the strand of which can be seen in the colobomata of the lens and iris (Mann).



(*a*) (*b*) (*c*)

FIG. 3.—Thin arcuate lens opacity in mongoloid. Case No. 54, aged 40 years. (*a*) Appearance with loupe. (*b*) Opacity seen by diffuse illumination with the slit-lamp microscope. (*c*) Optical section of lens with the slit-lamp showing opacity embracing the plano-convex areas in the deepest layers of the foetal nucleus.



(*a*) (*b*)

FIG. 4.—Two separate series of arcuate lens opacities in mongoloid. Case No. 53, aged 40 years. (*a*) Appearance with loupe. (*b*) Appearance with high magnification with the slit-lamp.

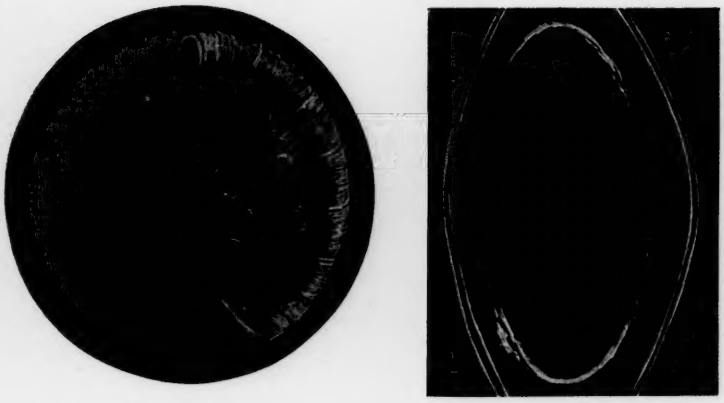
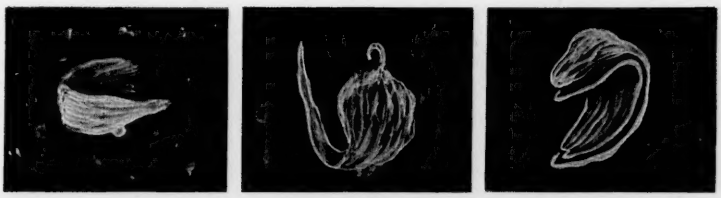


FIG. 5.—Curved lens opacities due to trauma found in one eye of a woman aged 29 years. History of being struck upon the eye by a cricket ball at age 12 years. Headaches and poor vision since 15 years. Slit-lamp shows opacities in outer layer of adult nucleus corresponding with age 12 to 15 years.



(*a*) (*b*) (*c*)

(*d*) (*e*) (*f*)

FIG. 6.—Arcuate lens opacities seen in mongoloids. (*a*) Case No. 34, aged 27 years. (*b*) Case No 61, aged 44 years. (*c*) Case No. 58, aged 43 years. Two concentric opacities are separated by a thin layer of clear lens fibres. (*d*) Case No 36, aged 41 years. (*e*) Case No. 17, aged 11 years. (*f*) Case No. 16, aged 11 years.

In (*e*) and (*f*) the arcuate opacities have developed into dense sector cataracts.

by means of a loupe and focal illumination (Fig. 3 (*a*))*. It forms an arch from the axis, curving around the equator of the foetal nucleus in the position that the periphery of the lens had attained at that stage of development. The smallest arcuate opacities are very narrow and relatively thin (Fig. 3 (*b*)). With the slit-lamp they are found just outside the plano-convex areas in the deepest parts of the foetal nucleus. They may be practically flat-surfaced or have a central rib—probably from the remains of the vessel. They then resemble minute curved white leaves near the centre of the lens.

Sometimes the opacity may be duplicated, the more superficial band being separated from the deeper (Fig. 6 (*c*)). Occasionally clear lens may cover the deep opacity and the two layers be more widely separated. In other cases several opaque strata are separated by zones of clear lens fibres. The more superficial opacities do not exactly conform to the deeper shapes, because within different layers there may be slightly varying amounts of clear and opaque lens fibres. Superficial arcuate opacities always occur within the same sector of the lens as those seen more deeply. Arcuate opacities are not found in the outer layers of a lens in the absence of opacities beneath them within the foetal nucleus.

A whole sector of a lens may appear opaque without any apparent differentiation into distinct layers. The opacity then extends from near the centre of the lens as a wedge. Usually only one sector is involved but no definite restriction occurs. Fig. 4 shows two different arcuate opacities within the same lens. Involvement of the whole circumference would result in a dense central cataract if only the cells within the foetal nucleus became opaque, or in a total cataract if no clear lens fibres formed as the lens increased in size. In no instance was there observed any coloboma of a lens, any displacement indicating disturbance of the zonule, or any sector defect of the iris or the pupil. In these respects the arcuate opacities of mongolism are very different from those attributed by Mann (1934, 1938) to the persistence of capsulo-pupillary vessels.

The other cataracts found in mongolism, namely opaque Y sutures and flake opacities, may or may not be present in the same lens that shows an arcuate opacity.

Cause of the Arcuate Opacities.—A most fascinating feature of ocular embryology is the formation and disappearance of the vascular capsule of the lens. During the earliest phases of development the cells receive their nutrition by diffusion from the

* For easy reference Figs 3 and 4 are reproduced from this author's article in this Journal (March, 1949, Figs 14 and 16).

uterus. With enlargement of the embryo and organ differentiation this supply becomes inadequate and blood vessels are provided.

The lens vesicle is able to separate and the posterior lens cells are able to grow forwards to form the primary lens fibres without vascular nourishment. The earliest secondary lens fibres envelop the primary lens fibres and meet to form the Y sutures (8·5 weeks) only a few days before the vascular capsule of the lens is fully developed (9 weeks). For the following two months the developing fibres are nourished by blood vessels in direct contact with the lens surface. Their nutrition is intimate and essential. But by the fourth month the posterior vascular capsule and the capsulo-pupillary vessels begin to regress (Mann, 1938). The lens is then supplied by a more distant source presumably the ciliary body.

If some of the capsulo-pupillary vessels were hypoplastic during the critical period of lens nutrition from about the eighth to the sixteenth week, it is conceivable that the cells dependent upon these vessels for their nutrition would be damaged. Those most likely to be involved would be the subjacent equatorial cells in the act of dividing and elongating at the time. Such defective cells cannot be shed, and remain throughout life to register the time of their derangement.

In mongolism the severity of the disturbance is insufficient to prevent division of the equatorial cells and thus cause a coloboma lentis, but it is intense enough to interfere with their ability to form clear lens fibres. Hence a sector opacity is produced without coloboma. If the deficiency were slight, only the lens fibres in active growth at the time of the damage need be opaque, those laid down subsequently could be clear. In this way a thin arcuate opacity would form indicating the size of the lens at the time of the disturbance. From knowledge of the times of formation of the zones of the lens, slit-lamp examination can determine when the disorder occurred.

In the lenses that show a recurrence of opaque layers interspersed with clear zones it may be supposed that the equatorial cells suffered permanent damage. When their nutrition was optimal they could lay down clear fibres, but when the favourable balance was disturbed, as by an intercurrent illness or metabolic upset, the lens fibres developing during that period would become opaque. With recovery, clear lens fibres would be formed again.

The character of any arcuate opacity therefore depends upon the degree of original damage to the equatorial cells, and upon the subsequent health of the individual.

The arcuate lens opacities associated with mongolism were found to originate deeply within the foetal nucleus arching around the plano-convex areas on the same level as the deepest Y sutures.

This situation corresponds with a lens size of about 8·5 or 9 weeks, *i.e.*, the beginning of the period of its nourishment by the capsulo-pupillary vessels.

Discussion

A hypoplastic vascular system is a characteristic feature of the syndrome known as mongolism. Postnatally this may be readily seen in the eyes by the poverty of the iris stroma, and generally by a very poor peripheral circulation. Defects of the heart and great vessels are common and indicate anomalous development, particularly about the end of the second month. The revelation of abnormal capsulo-pupillary vessels shows that defective vascular development is present in the early capillaries as well as in the heart and great vessels. This suggests that in mongolism the whole vascular tree is subject to defects in its earliest stages.

Two important concepts arise. First, the abnormal vascular system links with other developmental anomalies to show that the state of mongolism in the developing child is already determined by at least the third foetal month. Secondly, the presence of an inadequate vascular supply is a potent cause of secondary structural and functional defects, some of which help to characterize the syndrome of mongolism.

In the eyes the ultimate results of abnormal capsulo-pupillary vessels are diverse. Opacities in one sector of a lens cause gross astigmatism. If each lens is so affected, accurate fixation is impaired and a searching or ocular type of nystagmus results. Unilateral involvement may determine monocular vision, strabismus, and amblyopia. With the exception of high myopia, lens opacities are the commonest cause of strabismus in mongolism.

Other organs must be subject to similar hazards during their formation so that defects due to inadequate vascular supply should be widespread,

Unfortunately, we are ignorant so far of the cause of the vascular anomalies. This is probably the cause of mongolism itself. It is possible that numerous agents acting at the appropriate time and with suitable intensity can separately produce a similar end result. Since 1866, when Langdon Down first introduced the mongol nomenclature, innumerable theories have been propounded about the cause of this disease, but they are all unsatisfying and disappointment persists. Mongolism is a disease full of riddles made more difficult by many inaccurate observations and biased conclusions. The whole picture is still incomplete although adequate clinical material is readily available in mental hospitals. The

interpretation of many observations awaits more detailed knowledge of normal and abnormal growth processes.

Summary

Curved lens opacities may be found associated with persistence of a capsulo-pupillary vessel, after trauma, and in mongolism. Different types of mongoloid arcuate lens opacities are described and illustrated. The cause of these arcuate opacities is thought to be hypoplasia of capsulo-pupillary vessels. The position of the opacities in the lens indicates that mongolism is established by at least the third month of pregnancy. If abnormal vessels during development can cause such severe structural and functional defects in the eyes of mongoloids, it is possible that some of the other stigmata of this syndrome may be dependent on abnormalities of early blood supply.

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THE TRABECULA IN CHRONIC SIMPLE GLAUCOMA, WITH SPECIAL REFERENCE TO THE GONIOSCOPIC APPEARANCE OF BLOOD IN THE CANAL OF SCHLEMM*

BY

H. E. HOBBS

From the Glaucoma Clinic, Institute of Ophthalmology, London. Director of Research: Sir Stewart Duke-Elder.

GONIOSCOPIC observations of the iridocorneal angle in glaucoma have attracted increasing attention as the technique has developed and become more widely used. Attempts have been made to correlate certain clinical features with details of the gonioscopic picture and to classify types of the glaucoma symptom-complex according to these appearances (Sugar, 1941). The well established association between congestive attacks and a shallow anterior chamber has thus been illustrated by observations of the narrowness of the angle in a very large proportion of cases, and the demonstration *in vivo* of anterior peripheral synechiae after the attacks has confirmed the association of these with embarrassment of the aqueous outflow.

In chronic simple glaucoma the appearance of the trabecula, especially that part of it which overlies the canal of Schlemm, has been studied, and variations of the texture and pigmentation of its surface have been noted; these have been considered by some observers to signify the essential lesion in this type of glaucoma. Koeppe (1918), in early studies of the angle, first distinguished an appearance of pigmentation of the trabecula to which he attributed pathological significance in the genesis of glaucoma ; and his observation, if not his conclusions, was later confirmed by others, *e.g.*, Trantas, 1928. Pigment dispersal within the anterior chamber, however, was found to be a normal concomitant of age (Vogt, 1921), and trabecular pigmentation has since been considered to be so on the evidence of gonioscopic examination (Sugar, 1940; Busacca, 1945; François, 1948; Troncoso, 1947); but the appearances, more especially when the canal of Schlemm itself has been noted to be outlined by pigment in glaucoma, have continued to provoke speculation as to their possible role in the production of the disease. Thus Barkan and

* The expenses for this research were defrayed by the Alexander Pigott Wernher Memorial Trust.

others (1936) consider that a stoppage of the trabecular pores with pigment, allied with sclerosis of the trabecula itself, which they believe to be distinguishable gonioscopically by a porcelain appearance of the surface, is responsible for the great majority of cases of glaucoma simplex. Bangerter and Goldmann (1941) also find evidence of trabecular abnormality in glaucoma, either as a felted appearance of the surface or as pigmentation. They recognize such appearances with certainty in 55 per cent. of their forty cases of glaucoma simplex, and find similar, but less conclusive, changes in a further 30 per cent., only 15 per cent. appearing normal.

The fact that most observers have been able to see Schlemm's canal fill with blood during gonioscopy in a large proportion of normal eyes, but in only a very small proportion of eyes with simple glaucoma, has appeared to strengthen the case for a mechanical block at the angle of the anterior chamber. François (1948), for example, who finds no other gonioscopic sign pathognomonic, considers that the permanent and constant absence of blood from the canal in chronic simple glaucoma is the sole certain fact to be elicited from the examination; and Trantas (1928) finds this absence to be so constant that by the observation of blood he excludes the condition.

In normal eyes a red line at the site of Schlemm's canal, interpreted as blood, has been seen in a moderately large proportion of cases, either during observation with a contact gonioscope (Trantas, Salzmann, Busacca, François, etc.), or during hypotony induced by paracentesis, or after the use of a special form of dynamometer (Kronfeld and others, 1942; van Beuningen, 1949).

Personal Observations

Routine gonioscopic examination of patients attending the Glaucoma Clinic at the Institute of Ophthalmology has been performed with Goldmann's gonioprism and the Haag-Streit slit-lamp microscope, employing a minimum magnification of x 20. Forty patients with established chronic simple glaucoma provide the material for this analysis, and it may be of interest to record the findings in so far as they relate to the appearance of the trabecula. It has not been possible during these examinations to identify a difference in surface texture which appeared with any constancy among the cases in which the trabecula could be seen, but considerable differences in pigmentation have been noted; the cases include some in which little or none was present (" not marked "), some showing a moderate degree (" moderate "), some described as well-marked or with a good deal of pigment (" marked "), and

others in which the region of Schlemm's canal was clearly demarcated by a separate zone of pigment ("pigmented Schlemm").

Comparisons of the severity of the disease, as judged by the degree of cupping and extent of visual field changes, with the degree of pigmentation fail to show any association between marked trabecular changes and severe ocular lesions such as might have been expected if the latter were attributable to the former. Marked pigmentation was found with early clinical disease in several instances, and advanced clinical changes were present without remarkable pigmentation in others. These findings are summarized in the Table.

TABLE

Trabecular Pigmentation in Chronic Simple Glaucoma

"Not Marked"		"Moderate"		"Marked"		"Pigmented Schlemm"	
Case No.	Degree of Severity	Case No.	Degree of Severity	Case No.	Degree of Severity	Case No.	Degree of Severity
0003	great	0063	slight	0013	moderate	0066	slight
0044	moderate	0021	great	0020	great	0105	great
0089	great	0028	great	0023	slight	0126	slight
0107	great	0084	slight	0034	slight	0025	great
0037	moderate	0132	slight	0045	great	0085	great
0011	great			0068	moderate	0118	slight
0047	slight			0040	great	0056	slight
0071	moderate			0060	great	0134	moderate
0092	great			0128	slight	0018	moderate
0093	moderate					0008	great
0101	great						
0043	moderate						
0035	slight						
0123	moderate						
0125	moderate						
0135	slight						

It was noted that in four of the cases included in the Table, blood appeared in Schlemm's canal during gonioscopy, and no valid reason for this finding could be discovered so far as the state of the glaucoma was concerned. In view, however, of the pronounced differences noted in the fit of the gonioprism, pressure upon the post-limbal veins seemed likely to be greater in eyes in which the fit was scleral than in those in which the contact was primarily corneal. That this was likely to be a factor responsible for the appearance or non-appearance of the phenomenon was suggested

also by the fact that one of the cases in which blood was seen was a myope. It was felt, therefore, that the use of a gonioprism in which the fit could be said to be more certainly scleral in all cases might result in a greater proportion of cases showing the phenomenon, if post-limbal venous occlusion were a factor in producing the influx of blood into the canal. A simple modification of the Goldmann gonioprism was therefore made by adding to the scleral surface of its posterior lip a narrow rim, 0·75 mm. thick and 1·0 mm. broad, as shown in Fig. 1.

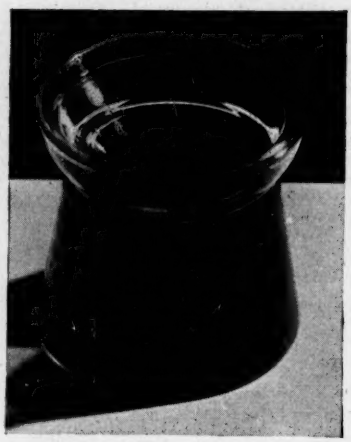

FIG. 1.—Modified gonioprism.

Examination of the normal eye with this device showed the canal to fill with blood (Fig. 2), the appearance being most readily apparent when the gonioprism was first applied with light pressure. When this was maintained for a few minutes the depth of colour increased and, in one or two cases, minute streams of blood were seen to issue from the canal into the anterior chamber. Firm pressure usually caused these to cease and the canal to blanch, an effect which could also be produced by gently withdrawing the gonioprism from the eye against the suction with which it adheres to the globe. Congestion of the episcleral vessels is apparent from the ring of oedematous conjunctiva seen on removing the instrument, and this is found to subside within a period of some 10 to 20 minutes. Further evidence of a rapid return to normality could be seen, in suitable cases, by the re-stratification of previously noted aqueous veins. It was felt, therefore, that the possibility of producing congestion dangerous to glaucomatous eyes was slight, and tonometry before and after examination supported this supposition, a maximal rise of 6 mm. Schiötz being seen in one patient only, and the majority showing an alteration, plus or minus, of less than 2 mm. Schiötz.

Examination in this way, of twelve normal individuals, whose ages ranged from 25 to 67 years, has shown blood in the canal in every case, either in its whole extent (7) or in sectors (5); and in two of this small number leakage of blood into the anterior chamber was seen.

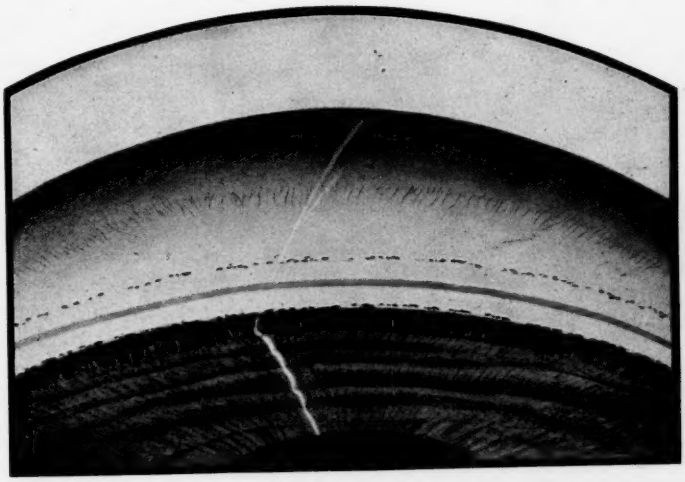

FIG. 2.—Appearance of blood-filled canal of Schlemm (initial magnification ×20).

In the 26 glaucomatous patients subsequently examined by this method, pigmentation of the trabecula was encountered in varying degree, associated in three instances with the definite appearance of blood in non-pigmented sectors, in four with a change of hue suggestive of blood, and in five others, more densely pigmented, with no such change. The findings in this respect may be summarized as follows :—

BLOOD FILLING THE CANAL	8
BLOOD FILLING SECTORS	8
APPEARANCES SUGGESTIVE OF BLOOD	5
BLOOD NOT SEEN	5

In three of these cases the minute leakages of blood noted in normal cases were seen to appear.

Discussion

The variations in the appearance of the trabecula are considerable and the difficulty, under the magnifications possible in gonioscopic examination, of recognizing an appearance characteristic of an insidious condition such as sclerosis must evidently be great. Nevertheless, since the cases examined included a number in which the condition was of long standing, it was to be expected that some of these, at least, would have shown a distinct variation from the normal and also from early cases of glaucoma. The failure to observe such an appearance would seem to provide reasonable evidence against its existence as an important factor in chronic simple glaucoma, as Sugar, Busacca, François, and others believe. Moreover, pigmentation of the trabecula does not appear to be a necessary concomitant of simple glaucoma, since it was absent in advanced cases, and marked in some with only early signs.

The number of cases of chronic glaucoma in which blood has been seen to enter the canal of Schlemm represents a sufficiently high proportion to cast doubt upon the contention, based upon gonioscopic evidence (Trantas, Barkan and others, Kronfeld and others, Bangerter and Goldmann), that obstruction at the canal of Schlemm plays an important part in the pathogenesis of the condition. In so far as transparency of the trabecula is necessary to the observation, it suggests that the opacification of the trabecula which would reasonably be expected to accompany sclerosis, and which has been put forward as an alternative reason for the non-appearance of blood in the canal, cannot be an important factor in many of the cases here reported. Busacca's finding, that in chronic simple glaucoma the trabecula preserves its normal transparency, through which he also has reported the appearance of blood, is thus confirmed.

Summary

(1) The gonioscopic appearance of the trabecula in forty cases of chronic simple glaucoma is reported. Among them the degree of pigmentation differed greatly, and no characteristic variation from the normal could be found, either in this respect or in the surface texture.

(2) There was no correlation between the degree of pigmentation and the severity of the disease; pigmentation was frequently found to be minimal in advanced glaucoma and it was marked in many cases in an early stage of the disease.

(3) A blood reflux into Schlemm's canal, seen with greater constancy when the gonioprism is modified to produce uniform scleral pressure, was noted in a high percentage of cases of chronic simple glaucoma.

(4) It is suggested that gonioscopic examination provides no conclusive evidence of the pathogenesis of simple glaucoma, and, in particular, that it fails to confirm the existence of a mechanical block at the angle of the anterior chamber by demonstrating either surface changes or the absence of blood reflux into the canal of Schlemm.

I should like to express my appreciation for the help which Mr. A. J. B. Goldsmith has given me in the preparation of this report.

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THE SIGNIFICANCE OF CONJUNCTIVAL ANEURYSMS IN DIABETICS*

BY

CLEMENT MCCULLOCH and T. J. PASHBY

From the Eye Department of the Toronto Western Hospital, and the University of Toronto, Ontario, Canada.

VASCULAR disease in diabetes remains a major problem yet to be solved. Retinal haemorrhages and retinal exudates have been considered diagnostic signs of diabetes and, although many have clung to the belief that these are arteriosclerotic or renal in nature, proof that they are diabetic in origin is accumulating.

Ballantyne (1943) demonstrated that some of the small spots of blood seen in the retina, which previously were considered haemorrhages, were actually aneurysms. He described them as being small, spherical forms attached to the finer perimacular venules like berries to twigs. He also demonstrated changes in the retinal veins, consisting of general and localized expansions, beading, loops, kinks, diverticula, fine new vessels on the surface of the retina, and new vessels projecting into the vitreous. He further noted fatty degeneration in the vessel walls, including the capillaries, and felt that ectasiae leading to aneurysms developed where the fatty changes were most marked.

Friedenwald (1948) added to our knowledge of these aneurysms by showing that the sacs were often incompletely lined with endothelium. He therefore assumed that the leakage of blood occurred first, and that the endothelium grew from the vessel to encapsule the blood. He stated that the process develops from a break in a capillary wall leading to a persistent slow leak of corpuscles; the hole shows little tendency to heal, but instead endothelial cells grow out to surround the extravasated blood cells. On the basis of this hypothesis, he suggested that hard white exudates could be explained as the consequence of still smaller breaks in the capillary walls through which plasma, but not red cells, escapes.

Ashton (1949) reported the post-mortem findings of 21 diabetics. The eyes, including the retina, iris, ciliary body, choroid, and conjunctiva, were examined for evidence of vascular changes. True aneurysms were found in the retina. One type of aneurysm showed an afferent and an efferent vessel; the basement membrane of the vessels extended into the wall of the aneurysm. Another type arose from one side of the vessel while the opposite side remained normal. No aneurysms were found in the iris, ciliary

* Received for publication April 4, 1950.

body, choroid, or conjunctiva, nor in the cerebral vessels, meninges, omentum, peritoneum, pleura, pericardium, bladder wall, liver, or kidney capsule.

Ashton noted the hyaline masses in the glomeruli in inter-capillary glomerulosclerosis, and felt that these masses and the retinal aneurysms were manifestations of the same pathological process modified by different anatomical structures. Although he did not find aneurysms in other parts of the body, he suggested that the hyaline masses in the glomerular tufts in inter-capillary glomerulosclerosis were occluded aneurysms.

The possibility of aneurysms being present in parts of the body other than the retina and glomeruli still remains despite their absence in Ashton's 21 autopsies. Aneurysms are difficult to see in sections. Only if the cut happens to pass in a certain plane does the distinction between vessel and aneurysm become apparent. In any given block of tissue the number of aneurysms may not be great, and many sections would need to be cut, and to be examined with the greatest care, before one aneurysm was found. Some other method, whereby larger areas of tissue can be quickly surveyed, is necessary before we can come to a decision concerning the presence of aneurysms in any particular tissue. The conjunctiva presents an opportunity for a relatively quick survey of a large area, and for accurate examination of detail. More than a year ago we noticed conjunctival aneurysms in diabetics, using the high power of the slit-lamp. We have endeavoured to determine the relationship of these aneurysms to diabetes. Other places in the body, such as the nailbed, may present opportunities for the study of aneurysms. We have, however, restricted our efforts to the conjunctiva.

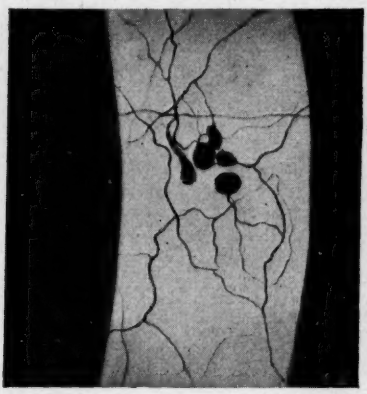

FIG. 1.—Conjunctival aneurysms in a diabetic.

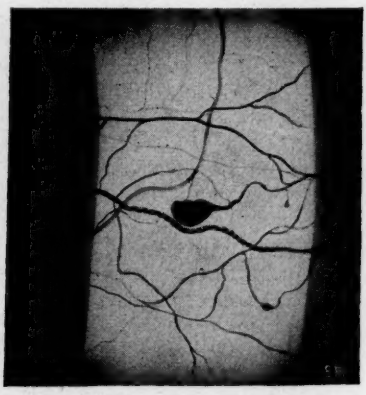

FIG. 2.—Conjunctival aneurysms in a diabetic.

Method

We studied approximately one hundred diabetics seen at the Toronto Western Hospital Diabetic Clinic, and on admission as in-patients. For controls we examined fifty patients who came to the eye clinic for routine refractions with no history of diabetes, or as in-patients with fractures, herniae, acute appendices, etc. We chose the controls from an age group to coincide with that of the diabetics. We charted the patients' age, sex, the duration of their diabetes, blood pressure, blood non-protein nitrogen, blood cholesterol, urine analysis for blood, albumin, and capillary fragility. The capillary fragility was estimated by placing a blood-pressure cuff just above the elbow, keeping it distended to 80 mm. Hg for five minutes, and counting the number of petechiae per square inch on the anterior surface of the forearm. The patients' eyes were examined, including the vision, conjunctiva, iris, lens, and fundus.

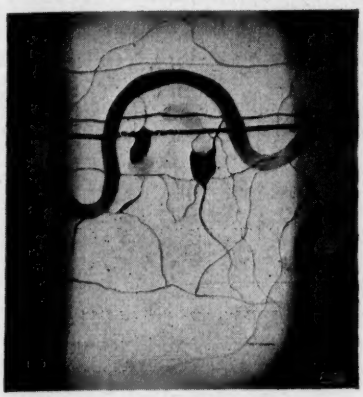

FIG. 3.—Conjunctival aneurysms in a diabetic.

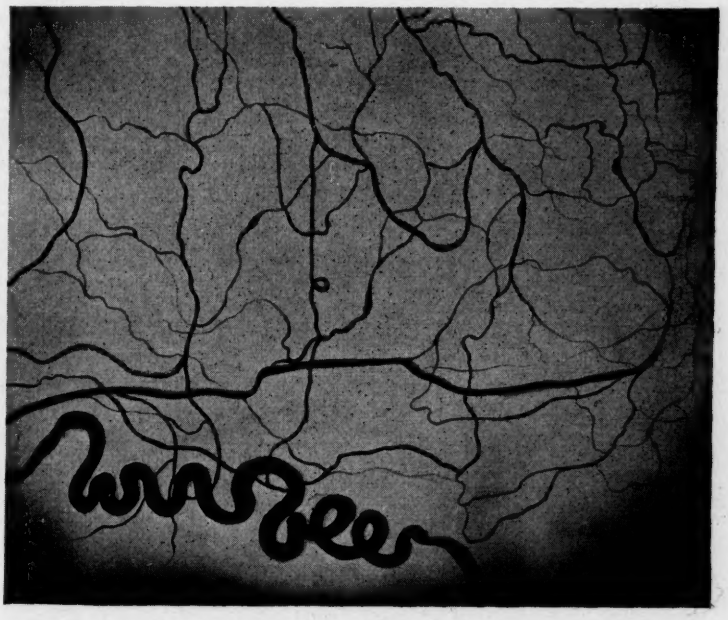

FIG. 4.—Conjunctival aneurysms in a diabetic.

Results

Conjunctival aneurysms were found in 55 per cent. of the diabetic and in 14 per cent. of the non-diabetic patients. The appearance of the aneurysms (Figs 1-4) is interesting. Two types can be identified. The first type is a true berry aneurysm, as described and seen by Ballantyne and others in the fundus, to which a vessel can, or cannot, be traced. These aneurysms are purplish in colour, as distinct from small haemorrhages which are bright red. The aneurysms have sharp borders, and round, smooth surfaces. They may be seen anywhere in the conjunctiva,

TABLE I

Groups		Diabetics				Normals	
		With Retinopathy (1)		Without Retinopathy (2)		(3)	
		Conjunctival Aneurysms	No Conj. Aneurysms	Conj. Aneurysms	No Conj. Aneurysms	Conj. Aneurysms	No Conj. Aneurysms
Average Age (years)		62	55	53	60	70	60
Average Duration (years)		13	13	5.5	6.1		
Average Blood Pressure (mm.Hg)	Systolic	168	151	130	154	139	140
	Diastolic	78	82	73	80	78	78
Albuminuria	+	1	3	0	1	0	3
	±	38	20	22	24	6	46
	−						
Benzidine	+	3	1	2	2	0	5
	±						
	−	33	19	16	24	6	46
Average Blood Cholesterol (mm. %)		196	239	201	223	160	176
Average Blood N.P.N. (mm. %)		42	46	40	40	45	47
Average Capillary Fragility (petechiae)		34	52	39	18	18	5

at the limbus or towards the fornix, and are either deep or superficial in the conjunctival stroma. They do not absorb but can be seen unchanged as to size, shape, and position after several months. This type we regard as the one which may be related to diabetes. The second type appears as an aneurysmal dilatation of the veins. It also can be seen anywhere in the conjunctiva, but is commonly found near an area of inflammation, as adjoining a pinguecula, and in old people presumably accompanying severe arterio-sclerosis. These dilatations are common, and, as we were doubtful of their significance, we did not include them in our records of aneurysms.

Other changes were noted which may or may not be associated with the aneurysms. Areas of haemorrhages into the subconjunctival tissue were seen. Some of the veins appeared dilated and tortuous, with sludging of the blood, and slowing of the flow. Aqueous veins were noted in many of the patients. Deposits of hyalin-like material were evident in the conjunctival stroma.

For the purposes of analysis we have allotted the patients to three groups of approximately fifty each, consisting of diabetics with retinopathy, diabetics without retinopathy, and normal individuals. The summary of the various findings is given in Tables I and II, and Fig. 5. All the findings can be considered negative, except that aneurysms were more frequently found in

TABLE II

Average Findings for Diabetics with and without Conjunctival Aneurysms.

Aneurysms	Sex	Age	Duration (years)	Blood Pressure		N.P.N.
				Systolic	Diastolic	
With	36 ♀ 19 ♂	55	9.1	139	78	41.2
Without ...	36 ♀ 8 ♂	57	9.3	152	78	46

Aneurysms	Chol.	Albuminuria	Benzidine	Cap. frag.	Lens	Fundi	V.A.
With	194	21 – 31 trace 1 +	43 – 4 +	39	25 + 29 –	33 + 21 –	20/56
Without ...	229	12 – 26 trace 5 +	38 – 4 +	16	12 + 27 –	21 + 45 –	20/42

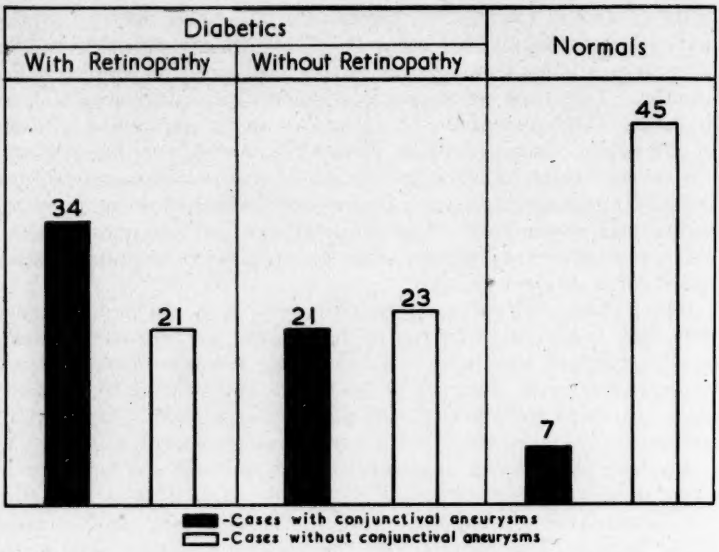

FIG. 5.—Relationship between conjunctival aneurysms and retinopathy.

diabetics with retinopathy than in diabetics without retinopathy, and in diabetics without retinopathy than in controls (Fig. 5).

Discussion

In this study, conjunctival aneurysms of the berry type were found four times as commonly in diabetics as in normal people. They were found in 62 per cent. of diabetics with retinopathy, and in 48 per cent. of diabetics with no retinopathy. The results are negative in all respects as regards age, duration of diabetes, blood pressure, albuminuria and haematuria, blood cholesterol and non-protein nitrogen, and capillary fragility.

In a previous report (McCulloch and Pashby, 1948) we found a relationship between diabetic retinopathy and age, and between retinopathy and duration of diabetes; but not between retinopathy and many other laboratory and clinical findings (Table III). Therefore it is not surprising that the presence of conjunctival aneurysms is not related to these many findings.

The 14 per cent. occurrence in normals is interesting. Aneurysms certainly occur in normals, hence their presence in the conjunctiva is not diagnostic but rather suggestive of diabetes. They may indicate a widespread tendency among the general population toward diabetes. The known hereditary character of diabetes (Joslin and others, 1947) suggests that such may be the case. We

TABLE III

Comparative Findings for Diabetics with and without Retinopathy.
(Study of 119 Diabetics, 1948)

Retinopathy	Age (years)	Sex (%)		Duration (years)	Severity (%)			Control (%)	
		♀	♂		mild	mod.	severe	good	poor
With ...	64	56	44	13	28	47	25	50	50
Without ...	62.5	48	52	7	22	53	25	37	63

Retinopathy	Serum Proteins			Proth. time (sec.)	Chol. (mg.)	N.P.N. (mg.)	Albuminuria (%)		Blood Pressure	
	total	alb.	glob. (mg.)				+	O	systolic	diastolic
With ...	7.1	4.15	2.8	15	160	42	50	50	160	91
Without ...	7.4	4.6	2.6	15	160	33	19	81	155	84

have seen two cases of massive aneurysms in the conjunctiva which were presumably due to angiomatosis. The patients were both young adult males, one diabetic and one not diabetic.

The presence of aneurysms in the conjunctiva suggests that they occur in most tissues of the body. The fact that aneurysms are seen in the retina and that changes of a similar nature can be found in the kidney, but have not been described in other tissues, implies that the aneurysms are present to a different degree in different tissues. The form which they take may vary slightly from one tissue to another.

The circulation to the middle layers of the retina, to the glomeruli of the kidney, and to the islets of Langerhans of the pancreas is similar (Beck and Berg, 1931; Dewitt, 1906; Bensley, 1911). The only vessels present in each are capillaries, which might be considered as a carefully segregated end-bed, designed to subserve the rapid transfer of metabolic products or fluid. This fact leads us to search for a similar pathological picture in these three organs.

The hyaline change which has long been known to occur in the islets of Langerhans (Opie, 1901) is of particular interest. In standard sections the material may appear as a thickening of the reticulum, as small round balls, as larger masses, or as a complete replacement of the islet tissue by hyalin (Figs 6-9, overleaf). The

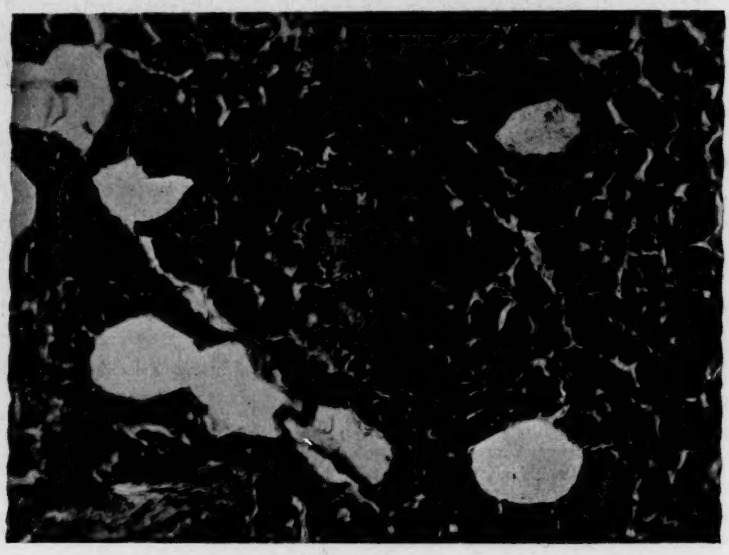

FIG. 6.—*Islet of Langerhans from a case of diabetes. Taken at autopsy.* Haematoxylin and eosin stain.

FIG. 7.—Islet of Langerhans from a case of diabetes. Taken at autopsy. Haematoxylin and eosin stain.

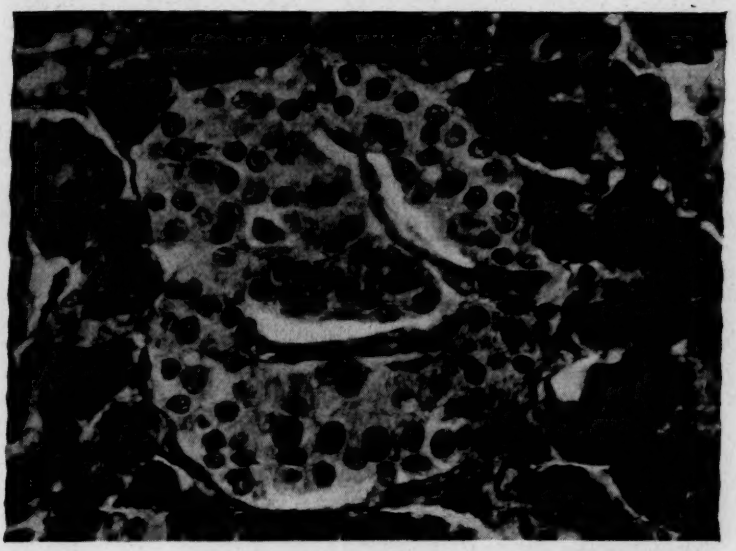

FIG. 8.—Islet of Langerhans from a case of diabetes. Taken at autopsy. Haematoxylin and eosin stain.

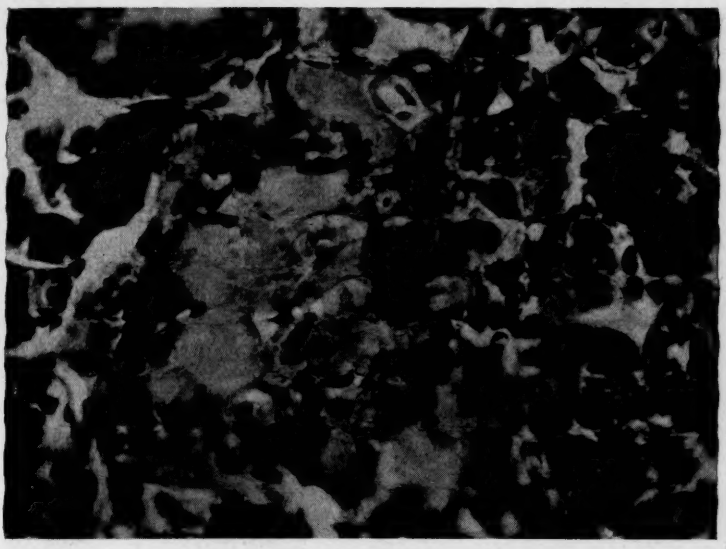

FIG. 9.—Islet of Langerhans from a case of diabetes. Taken at autopsy. Haematoxylin and eosin stain.

hyalin might come from degeneration of the islet cells or as overgrowth from the capillary walls. The latter possibility suggests that the hyaline changes in the pancreas, in the glomerular tufts, and in the retina, are comparable. All three changes may be considered as an increase in the intercellular ground substance. In the retina it appears as hyaline changes in the walls of microaneurysms, in the kidney it appears in the glomeruli as hyaline masses, and in the pancreas it appears in the islets in whorls and balls next to the vascular clefts. This increase in intercellular substance would decrease the blood supply of the islets, decrease the adsorption of substances from the blood, and decrease the transfer of insulin into the blood.

The hyaline changes may be the cause of diabetes. Our experience, and that of others (Waite and Beetham, 1935; Wagener and others, 1934) has shown that the retinal lesions are not directly related to the diabetes. Severe retinopathy may be seen in patients with mild diabetes of short duration, under good control. Similarly one may find no retinopathy in patients with severe diabetes of long duration, and under poor control. This lack of correlation finds explanation if we consider the hyaline changes in the pancreas as a cause of the diabetes. Then diabetes is seen as a general vascular disease of which the changes in the pancreas are only a part. If the vascular change is more advanced in the retina than it is in the pancreas, the retinopathy would outstrip the severity of the diabetes. On the other hand, if the vascular change is more advanced in the pancreas, severe diabetes would be possible with little or no retinal change. The development of intercapillary glomerulosclerosis in some patients, but not in others, can be similarly explained. Finally, the presence of conjunctival aneurysms demonstrates the widespread character of this disease.

Conclusion

Aneurysms can be found in the capillaries of the conjunctiva, and are related to the presence of diabetes, and to the incidence of diabetic retinopathy. Diabetes may be part of a generalized vascular disease which affects the retina, glomeruli, islets of Langerhans, and conjunctiva.

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INTRA-OCULAR INVOLVEMENT IN A CASE OF XANTHOMATOUS BILIARY CIRRHOSIS*

BY

NANCY LEWIS

Melbourne, Australia

XANTHOMATOUS biliary cirrhosis is described by Thannhauser (1940) as a form of primary essential xanthomatosis of the hypercholesterolaemic type, the characteristic features of which are the occurrence of biliary cirrhosis; a high total cholesterol content of the blood without a milky serum; and the development of skin xanthomata plana and tuberosa. The skin lesions show a particular distribution in the creases of the palms and soles, on the extensor aspects of the elbows and knees, and over the Achilles tendon. Fluctuating jaundice of long duration is the most outstanding symptom and may lead to a faulty diagnosis of occlusion of the common bile duct by stone or neoplasm. The obstruction, however, is not complete and stercobilin is to be found in the pale faeces. The liver is enlarged and so, usually, is the spleen. The bile acids and bilirubin content of the blood are raised, the alkaline phosphatase is very high, and the serum protein normal. Although the skin of the eyelids is involved by xanthelasma no description of other ocular manifestations can be found in the literature and therefore the following case is reported.

Case Report

Mrs. B., aged 47 years, began four years ago to suffer some upper abdominal pain, which was followed by the appearance of jaundice and pruritis. Her liver was enlarged and clay-coloured stools were observed. Two years ago xanthelasma appeared on her eyelids and later xanthomata plana in the creases of fingers and toes. Recently she has lost some weight.

Liver biopsy two years ago showed slight increase of small round cells and fibroblasts in the portal tracts.

On present examination, she has rather a dusky greenish-yellow colour of the skin with xanthelasma over both upper and lower eyelids (Fig. 1), with xanthomata plana in the skin creases of the fingers and toes (Fig. 2), and xanthomata tuberosa over both olecranon processes (Fig. 3) and behind the Achilles tendon. She has a punctate ulceration due to scratching of the body.

The liver is enlarged but the spleen is impalpable. The urine is bile-stained and contains pigment with no increase of urobilin. The faeces are clay-coloured, stercobilin is present, and occult blood has not been detected.

The results of liver function tests may be tabulated as follows:

Serum bilirubin increased.
Hippuric acid excretion, 1·3 g. in 4 hours.
Cephalin flocculation test, + + +.
Alkaline phosphatase, 42 units (King Armstrong).

* Received for publication October 24, 1949.

Fig. 1.—Patient showing jaundice and xanthelasma of eyelids.

FIG. 2.—Xanthomata plana occurring along the skin creases of the fingers.

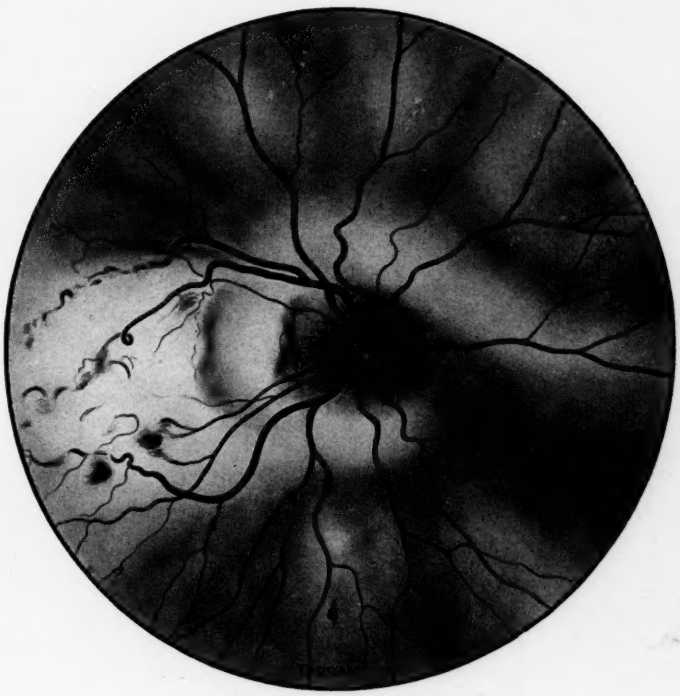

FIG. 4. Appearance of right fundus.

Total serum protein, 6·5 g. per cent.
albumin, 3·6 g. per cent.
globulin, 2·9 g. per cent.
gamma globulin, 1·34 g. per cent.
Prothrombin index, 91 per cent.
Bile in urine, pigment, ++; salts, +.

The results of other investigations are as follows:
Blood normal, Hb 98 per cent.
Blood cholesterol, 530 mg. per cent; serum clear, not milky.
Biopsy of a nodule from the elbow showed a collection of cells containing fatty droplets—reported xanthoma.
All other general investigations were negative.

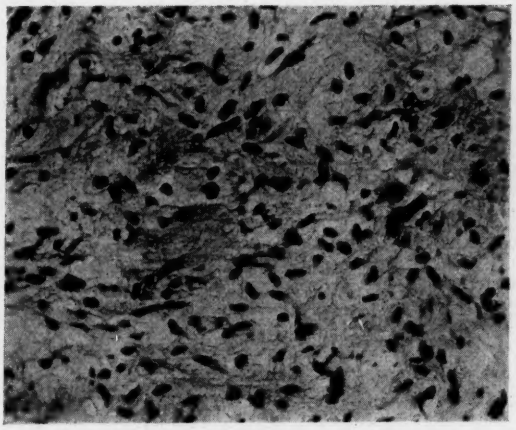

FIG. 3.—Photomicrograph of medium view of a section of xanthomatous tissue removed from the skin over the olecranon process showing typical xanthoma cells.

The patient has submitted to four abdominal operations and laparotomy has failed to reveal any extra-hepatic biliary obstruction. The liver function tests give results suggesting diffuse hepatic damage and there is only a trace of bile entering the bowel. Changes shown at liver biopsy were those of biliary obstruction of biliary cirrhosis rather than those of chronic viral hepatitis or of nutritional liver disease. The raised blood cholesterol and section of the nodule confirm the diagnosis of xanthomatous biliary cirrhosis as described by Thannhauser.

Ocular Symptoms.—These began six months ago with some impairment of vision of the right eye. She noticed what appeared as a floating cloud which persisted for six weeks and then cleared. This was followed by flashes of light three months ago, which were present at all times but were worse in the daylight, and were seen over the whole field of vision. Since then her sight has gradually failed.

Results of examination:
Right eye divergent and conjunctivae icteric.
Vision, right—perception of light only, projection being faulty.
left—6/9 with correction.
Right pupil shows sluggish reaction to direct light but reacts normally to the consensual light reflex.
Left fundus appears normal.

In the right eye can be seen widely scattered yellowish areas involving all parts of the fundus (Fig. 4). These yellowish patches are deep to the retinal vessels, which appear normal except where displaced forwards by the larger collections. The yellowish areas vary in size from fine dots to larger confluent masses. The largest mass forms an extensive tumour involving the lower temporal one-sixth of the fundus, and producing detachment of the retina over it. The retinal vessels in this situation are broken up peripherally, and haemorrhages with oedema of the retina are present. There is also retinal pigmentary disturbance consistent with its displacement by these collections. The disk margins are indistinct owing to the presence of the surrounding swellings.

Although it has not been possible to section the eye, it may be assumed that there are xanthomatous collections in the fundus similar to the xanthomata present elsewhere in the body.

Summary

A case of xanthomatous biliary cirrhosis is described with involvement of the eye by probable xanthomatous tissue.

I should like to thank Dr. Ian Wood of the Walter and Eliza Hall Institute for permission to report this case, Dr. Doig for supplying the clinical notes, Mr. Inglis, clinical photographer at the Royal Melbourne Hospital, for his assistance with the photography, and the Medical Illustration Department of the Institute of Ophthalmology, London, for the painting of the fundus.

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A CASE OF WATERING EYE DUE TO PTERYGIUM*

BY

F. J. DAMATO

Malta

PATIENTS suffering from pterygium do not usually complain of anything. Advice is generally sought because the patient is told by his friends that something, a piece of skin, is growing on the eye. In Malta, pterygium is popularly known as " karnita ", octopus. The patient is very upset by the information that this marine inhabitant is gnawing at the eye, and soon asks for treatment. The particular interest attaching to this case was that epiphora was the chief accompanying sign of pterygium.

Fuchs (1917) gives a masterly and detailed description of pterygium. No mention is made of lacrimation. Duke-Elder (1938), De Schweinitz (1913), and Gifford (1938), say nothing about pterygium as one of the causes of watering eyes.

Case Report

G. C., 44 years old, a dockyard fitter, came to consult me on July 26, 1949. He said that his eyes were watering as they once used to do when he was suffering from pterygium. He had been operated upon for pterygium in the right eye in 1941 and in the left eye in 1943.

On examination, pterygia were found on the nasal side in each eye. That in the right eye was large and fleshy, and extended to within 3 mm. of the corneal centre. Closer observation revealed that the upper lid margin, medial to the upper lacrimal punctum, was attached to the pterygium and that the punctum was displaced inwards.

Vision R.E. c−1·5 ax., 90=6/5.

Vision L.E. unaided, 6/

No evidence of trachomatous changes.

I performed a McReynold's transplantation on the right eye and severed the connection between the lid margin and the pterygium. The conjunctival wound healed well and the patient was completely relieved of the lacrimation. The pterygium in the left eye was transplanted a week later.

Three months later the right eye had started to water again. Examination of the eye revealed a jelly-like mass, flanked by granular tissue, covering the site of the old pterygium. The inner angle of the lid margin was once more adherent to it. This time, I covered the bare area left over after excision of the pterygium, by bringing from above and below two-tongue-shaped strips of conjunctiva which I sutured together in the horizontal meridian. The wound healed well and when seen five months after the last operation the pterygium had not recurred, and the eye had stopped watering. The upper lid margin had remained completely free.

One might think that the epiphora was due to the existence of the fleshy pterygium, adherent to the upper lid margin, with deviation of the upper lacrimal punctum, or perhaps to the fact that the presence of a fairly large mass in the lacus lacrimalis hindered the normal flow of tears to the lacrimal punctum. I have made a point of asking all patients suffering from pterygium about watering eyes. Four of them have answered that it was a watering eye that made them aware that there was something wrong.

* Received for publication May 5, 1950.

Some observations on the aetiology and surgery of pterygium will not be out of place. Climatic conditions are important factors. Continuous and violent gusts of wind with their usual accompaniment of hard, stony dust are a frequent occurrence in this island. Pterygium is rather common here, and my impression is that it is usually found in people who spend a good part of the day in the open air. However, I have seen it in quite a number of housewives who are most of the time indoors.

All the cases I have seen were on the nasal side, except one. In this particular case, there was a pterygium on the nasal side in the left eye, and in the right eye, a pterygium on the nasal side reached to within 2 mm. of the corneal centre, and another one on the temporal side also extended to about 2 mm. from the centre. A narrow pupillary area remained free. Vision in this eye was reduced to 6/18. The patient, an old man aged 70 years, has been suffering from pterygia in both eyes for 15 years.

I have found McReynold's transplantation a satisfactory operation. In a consecutive series of over fifty cases, two pterygia recurred. I have been using Herbert's keratome 3·5 mm. wide, which is easier to handle than either a Graefe knife or a scalpel, to dissect the apex and body of the pterygium from the corneal surface. It is necessary to remove the episcleral tissue of the bare area which remains after transplantation of the pterygium, and to cover it by pulling the adjacent conjunctiva on to it by one or two stitches.

Nobody in Malta would ever dream of consulting an ophthalmic optician to have his eyes tested for glasses. Everybody goes to the eye doctor. A great many people, however, still ask for the services of old women who, for ages, have been reputed to be able to remove pterygia by means of a shell, which is popularly thought to be extracted from the head of the octopus, but is really the operculum of Trochus Rugosus, a salt water snail found in the Grand Harbour. The ophthalmic surgeon is only consulted when, in spite of the magician's efforts, the " octopus " is seen to be still clinging to the eye.

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APPLIANCES

A NON-MAGNETIC FOREIGN-BODY EXTRACTOR*

BY

H. B. STALLARD

London

IT is now known that some non-magnetic metal alloys do not remain inert when lodged inside the eye. When such a foreign-body causes irritation, and also when its position in the vitreous seriously interferes with vision, its removal is necessary and justifiable.

The surgical approach is through a scleral incision and the instrument passed through this is guided to the foreign-body under ophthalmoscopic view.

The disadvantage of cross-action forceps for this purpose is that some vitreous is likely to leak through the scleral incision and to pass the shanks of the forceps when the jaws of this instrument are opened.

An alternative is to use a wire-snare made from a hypodermic needle style, the loop of the snare projects from the lumen of an intravenous needle the point of which has been cut off. The free ends of the snare are controlled where these leave the other end of the needle, held in the operator's hand. It is often difficult to engage the snare over the foreign-body and to hold it securely whilst withdrawing the instrument from the vitreous.

It is therefore desirable to have an extractor which :

(1) takes up the minimum of room,
(2) has neat lines with the extractor jaws flush with the hollow shaft through which they pass.
(3) is easy to manipulate without moving the shaft of the instrument,
(4) has a shaft which will exactly fit the scleral incision, thus allowing no leakage of vitreous whilst the instrument is in the eye. The incision in the sclera is made equal to the circumference of the shaft.

Instrument

Fig. 1 shows two sizes of an extractor, one open and the other closed, which I designed during the 1939-45 war. It consists of a hollow shaft, 3 mm. in diameter in one size and 1·5 mm. in the other. Through the shaft passes a steel style and the free end of this is split and fashioned to form two spring jaws with concave opposed surfaces roughened by criss-cross grooves. The tip of each jaw is slightly inverted for better retention of the foreign body. The slot on the handle advances and withdraws the spring-jaws from and into the hollow shaft. The jaws are withdrawn into the shaft for passage through the scleral incision and through the vitreous to the site of the foreign body when the slide is moved forwards under ophthalmoscopic view so that the jaws may open and envelop the foreign body. The jaws are then withdrawn by moving

* Received for publication March 10, 1950.

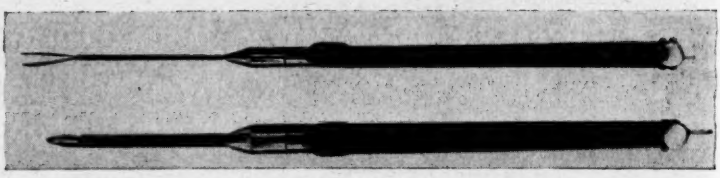

FIG. 1.—Extractors made by Down Bros., and Mayer and Phelps, Ltd.

the slide backwards and in so doing close over the foreign body and hold it either around or within the entrance of the hollow shaft.

Technique

The site on the sclera is chosen which gives best access to the foreign body, and in front of this a conjunctival flap is cut with an incision convex towards the limbus. The flap is held reflected by two sutures of 0 black silk which are clamped to the head towel. Diathermy, 80 milliamperes for 5 seconds is applied to the sclera at the site for incision. The length of the incision is carefully measured and marked in gentian violet. The eye is steadied with a scleral hook inserted just in front of the anterior limit of the incision. Half the thickness of the sclera is incised with a No. 15 Bard-Parker knife. The edges of the scleral incision are now retracted by scleral hooks and an interrupted suture of 000 black silk, knotted at one end, is passed across the wound. The knot is drawn against the sclera and that part of the stitch which traverses the wound is pulled out into a loop, the arms of which are held in two pairs of plane forceps so as to retract the edges of the wound (Fig. 2). The scleral incision is now completed down to the choroid with the tip of a small cataract knife. The head is turned so that the scleral wound may be uppermost, a quick stab incision is made through the choroid and retina with a cataract knife, and the foreign-body extractor is immediately introduced through this so that its shaft fits the scleral wound exactly before any vitreous appears. The head is now gently turned so that the eye looks in the primary position, that is up to the ceiling. The surgeon holds an ophthalmoscope in his other hand, which is covered with a sterile linen glove.

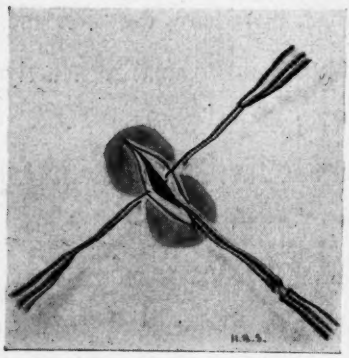

FIG. 2.

The extractor is passed across the vitreous with the jaws closed and flush with the shaft. In this position the jaws make a blunt point which is aimed deliberately behind the foreign body to allow for the refraction of the vitreous. To avoid pushing the foreign body about in the vitreous just in front of the tips of the extractor blades, and so being unable to grasp it, it is well to open the blades behind the foreign body and then swing these forward to engage it. The slide on the handle is moved back and the jaws close on the foreign body. When a secure grasp is obtained the shaft of the instrument is drawn to the scleral incision. It is essential to cause the minimum of disturbance in the vitreous. Frequent thrusts through it with the extractor damage its structure and render the field around the foreign body increasingly turbid. Immediately the tip is clear of the sclera, the scleral suture is pulled upon quickly to close the wound at once. There should be little or no vitreous loss for the shaft of the extractor fits the scleral incision exactly, the length of the incision being equal to the circumference of the shaft. The suture is then tied with a surgical knot, penicillin is instilled into the wound, and the conjunctival incision is closed with a continuous key-pattern suture.

DARK GLASSES

BY

F. A. WILLIAMSON-NOBLE

London

DARK glasses for use after intra-ocular operations present rather a problem. The desiderata would appear to be cheapness, lightness, comfort in wear, and exclusion of extraneous light. These were fairly well met before the war by dark glasses with perforated metal side-pieces which came from abroad. Having a flexible frame and side-pieces, they could, by judicious bending and twisting, be made to fit anyone.

These glasses are not procurable now, however, and one has had to rely upon heavier and more expensive types which are not malleable and often require padding with cotton wool or rubber tubing to make them comfortable. It occurred to me that the eye-shield made in large numbers during the war might be useful, if it could be suitably tinted. This was done, but the result was unsatisfactory because of poor ventilation and a tendency for the shield to cockle up. Ventilation was improved by replacing the lateral portions of the shield with fine wire mesh (Fig. 1), and protective goggles of this type could be worn by patients with a fair degree of comfort. The cockling problem still remained, however, and distortion rendered the goggles unsatisfactory after a few days of wear. This difficulty was surmounted by inserting a small piece of metal into the cloth joining the tinted plastic material to the wire-netting side-pieces (Fig. 2); at the same time the buckle was moved so that it lay at the side of the head, instead of at the back, where it was apt to cause discomfort to a patient lying with the back of his head in contact with the pillow. These goggles have been used by patients with satisfactory results and are relatively inexpensive.

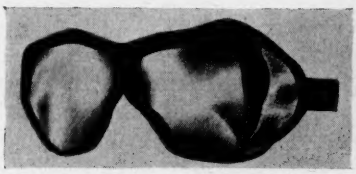

FIG. 1.

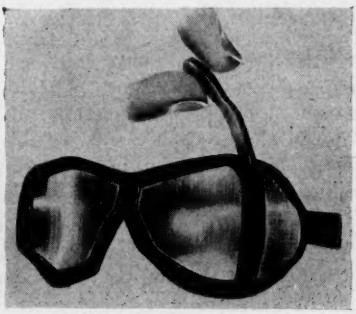

FIG. 2.

I am grateful to Messrs. Theodore Hamblin for their kind co-operation in making these goggles.

BOOK NOTICE

Thérapeutique Chirurgicale Ophtalmologique. By C. DUVERGER, E. VELTER, and P. BRÉGEAT. Pp. 464, 62 figs., 44 plates. Masson et Cie, Paris. 2nd. ed., 1950.

The aim of the authors in producing a second edition of "Thérapeutique Chirurgicale Ophtalmologique" is to describe the indications and techniques of those procedures which, from their own experience, they consider safe and sound. Throughout the book the reader is aware of this personal discrimination, which confers a directness upon its councils and an economy of language unusual in text books of ophthalmic surgery.

The authors discuss in a practical way all aspects of their subject from the details of removal of a chalazion to the intricacies of the transcranial approach to the orbit. The choice of procedure for everyday conditions is sometimes different from our own. The use of the keratome in cataract surgery, and of the Graefe knife in glaucoma iridectomy, the preference for the Lagrange operation in glaucoma, the implantation of the femoral head of infants into Tenon's capsule, the emphasis on regional anaesthesia about the face, and the recommendation of chloroform on the odd occasion when a general anaesthetic is thought necessary, are a few examples. The routine methods both in France and Britain, however, are basically similar.

Since the first edition 24 years ago, keratoplasty, intracapsular extraction, and the treatment of detachment of the retina, have been developed, and they receive adequate attention in the new edition. The coloured plates in this volume are quite outstanding, not only for their accuracy in surgical detail but also for their faithful colours. The many line drawings are clear and boldly executed. In short, this is an excellent product of French Ophthalmology and both authors and publishers are to be congratulated on making such a welcome addition to our library.

CORRESPONDENCE

CAVERNOUS SINUS THROMBOPHLEBITIS

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS—Dr. A. Miklós' article, "The Cure for Cavernous Sinus Thrombophlebitis", in the *British Journal of Ophthalmology* (1950), **34,** 235, merits our heartiest congratulations. I am sure that I would readily pursue a similar therapeutic course under the described conditions, but since intrathecal medication is apparently frowned upon in our country, it might be worth while to point out some comments upon this therapeutic approach as demonstrated in a paper by Wilson, Rupp, and Wilson in the *Journal of the American Medical Association* (1949), **150,** 1076. In this paper, entitled "The Dangers of Intrathecal Medication", the authors have stated,

> "The injection of any foreign substance into the subarachnoid space produces an aseptic meningeal reaction characterized principally by pleocytosis and increased protein content."

They believe that neurologic complications occur more frequently when the neural tissue is already damaged. They, furthermore, refer to a series of 51 patients with conditions other than primary disease of the central nervous system in which the electro-encephalogram was found to be abnormal in more than 60 per cent. even when penicillin was administered only systemically.

In the author's second case only 60,000 units of penicillin had been administered intramuscularly after which it was decided to use penicillin intrathecally since the patient was getting worse. Miklós states:—

> "Barton and others (1947), however, have found that with a normally permeable blood-brain barrier the usual 20,000 to 50,000 units of penicillin administered intramuscularly are not detectable in the spinal fluid, and that if the desired bacteriostatic concentration is to be attained, 600,000 to 1,000,000 units must be given intramuscularly."

Since it has been suggested that one should remember that the haemato-encephalic barrier is diminished in disease of the nervous system, and adequate diffusion may occur under pathologic conditions even though permeability is inadequate in normal experimental subjects, there may still be some difference of opinion regarding this permeability. However, the use of 600,000 to 1,000,000 units of penicillin intramuscularly initially as used by many in the United States may avoid the dangers of intrathecal medication.

In conclusion, Wilson, Rupp, and Wilson state:

"There is no doubt that intrathecal injections of drugs, anaesthetics and antibiotics produce neurologic complications in many cases."

Sincerely yours,

EMANUEL ROSEN.

692 HIGH STREET,
NEWARK, N.J., U.S.A.
May 2, 1950.

NOTES

INSTITUTE OF OPHTHALMOLOGY

THE new term commences Wednesday, October 4, 1950. The inaugural address will be given by Dr. Russell Brain, President of the Royal College of Physicians; his subject will be "Endocrine Exophthalmos". This will be followed by the annual dinner at Claridges at 7.30 p.m. Tickets, price 25*s.* may be obtained from the Secretary at the Institute.

Past students of the Institute and of the Moorfields, Westminster and Central Eye Hospital are cordially invited to attend.

Honours

DR. H. ARRUGA of Barcelona has been created a count by the Spanish government.

Fellowships

ON the occasion of the XVI International Congress of Ophthalmology the Royal College of Surgeons of Edinburgh conferred Honorary Fellowships upon Dr. H. Arruga of Barcelona, Sir Stewart Duke-Elder, and Dr. Alan C. Woods of Baltimore; and the Royal College of Surgeons of England conferred Honorary Fellowships upon Dr. P. Baillart of Paris, and Dr. Derek Vail of Chicago.

At its Annual Meeting on July 24 the Société Française d'Ophtalmologie conferred an Honorary Fellowship upon Sir Stewart Duke-Elder.

Death

We regret to announce the death of Dr. C. M. Stevenson of Cambridge.

ADDENDUM

The author of the article "A Plastic Disk for Retention of a Corneal Graft", which appeared in the July issue of the B.J.O. (p. 450), wishes to acknowledge Messrs. Theodore Hamblin, Ltd., as the makers of the acrylic disk as illustrated.